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OCULOMOTOR CONTROL IN CHILDREN WHO WERE BORN VERY PREMATURELY

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Abstract

Advances in medical technology have meant that increasing numbers of preterms are surviving and there is recent evidence that the number of preterm births is also increasing. Preterm survivors are at increased risk from a variety of visual, cognitive, behavioural, motor and specific reading deficits; these are by no means only experienced by the minority of preterms with major neurological impairment. Many of these deficits are attributable to an increased incidence of cerebral lesions in preterms including periventricular leukomalacia, intraventricular haemorrhage, a reduction in cortical volume and lesions affecting the caudate nucleus, cerebellum and thalamus. These cerebral structures (caudate, cerebellum, thalamus and cortex) provide the neural substrate for the oculomotor control system, yet there is a paucity of research on the control of eye movements in children born preterm. Therefore in this study the monocular and binocular control of eye movements, the development of antisaccade and vergence control and the association between both oculomotor control and visual/binocular function with reading difficulties was investigated in children born very preterm with normal IQ (≥85), who were free from major neurological deficits. In general the control of saccades in preterms did not differ significantly to full terms, though preterms had a larger range of saccade gain and latency. Pursuit latency was longer in preterms, but the differences between the groups were modest. There were no statistically significant differences between the groups in pursuit acceleration. One of the main areas of deficits in preterms was in the control of antisaccades. Preterms had statistically significantly higher directional error rates, a tendency for shorter antisaccade error latencies and a greater proportion of express antisaccade errors. Vergence initiation was also impaired in preterms with statistically significantly longer latencies. Other aspects of vergence control were similar for both groups. The control of binocular saccades and fixation also showed no differences between preterm and full term children. Longitudinal and cross-sectional assessment of the development of antisaccade and vergence control revealed that at 13 to 14 years of age there were no longer any differences in antisaccade performance between preterm and full terms, but vergence latencies were still longer for preterms. At 15 to 16 years, antisaccade error rates had reduced for both groups, though preterms had a higher residual rate. Vergence latencies also reduced in both preterms and full terms and were now similar for both groups. Reading assessment revealed that a substantial proportion of preterms (age 8-11 years) had a specific reading difficulty. Visual and binocular function measures did not differentiate between preterms with and without reading difficulties. Preterms with reading difficulties had larger saccade gain for rightward saccades, a higher proportion of express antisaccade errors, shorter latency of antisaccades and a higher velocity for square wave jerks, than those without reading difficulties. The main deficits in the preterms in this study were therefore in the areas of antisaccades and vergence, both of which have a long developmental period. These results are consistent with subtle frontal cortical damage or disrupted or delayed maturation of frontal structures. Oculomotor deficits are unlikely to be the cause of the reading difficulties in preterms, but may be associated with the reading problems as well as other behavioural disorders known to affect preterms such as executive dysfunction. If the oculomotor impairments prove to be predictive of executive dysfunction and reading difficulties, the simple oculomotor tasks used in this study would be a useful assessment to help with the early identification of these behavioural issues, which may assist with the early implementation of intervention or treatment programmes. This area needs to be explored in the future.

Oculomotor control in children who were born very preterm

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Glossary

Accommodative facility

The ability to exert and relax accommodation repeatedly, usually assessed within a specific time period.

Antisaccade

A voluntary saccade made in the opposite direction to the appearance of a target.

Corollary discharge

It is postulated that the cerebellum governs saccade accuracy by monitoring motor commands, via copies of the commands themselves. These copies are referred to as the corollary discharge or efference copy signals.

Emmetropisation

At birth most infants are hypermetropic. This refractive error reduces during the first two years of life during a process known as emmetropisation.

Executive function

This refers to a collection of interrelated processes that are responsible for purposeful and goal directed behaviour and involves the elements of anticipation, goal selection, planning and organisation, initiation of activity, self-regulation, mental flexibility, deployment of attention, working memory and utilisation of feedback.

Express saccades

Short latency (90-140ms) reflexive visual saccades that are elicited during a gap task.

Gap task

A task where the fixation stimulus is removed early (i.e. before the target appears), which allows disengagement of the fixation system

Main sequence

The duration and peak velocity of saccades can be characterised by their stereotypical broadly linear relationship with saccade amplitude. This fixed relationship is referred to as the main sequence.

Major neurological deficit (preterms)

A major deficit such as cerebral palsy, blindness or deafness.

Oculomotor control

The cortical and subcortical control of eye movements.

Open loop (pursuit)

Pursuit acceleration between 40ms and 100ms depends on the target's velocity, position, movement direction and contrast. There is no visual feedback during the first 100ms of pursuit and this is known as the open loop period.

Post-saccadic drift

This refers to the drift that occurs at the end of a saccade, which is usually in a convergent manner and is the result of mismatching between the pulse and step components of the saccade.

Prism fusion blur point

The point during a fusion range assessment when the subject has used all available fusional reserves and uses accommodative convergence in order to keep the target fused.

Prism fusion break point

The point during a fusion range assessment when the subject has used all available fusional reserves and accommodative vergence, resulting in the break of fusion and diplopia.

Saccade gain

The amplitude of the actual saccade/amplitude of the desired saccade i.e. target amplitude.

Saccadic disconjugacy

The difference in saccade amplitude between the eyes that occurs both at saccade onset and during the saccade.

Smooth pursuit gain

The actual pursuit velocity (usually assessed with a sinusoidal moving target)/actual velocity of the target.

Specific reading difficulty

A reading difficulty that occurs in the presence of a normal IQ.

Abbreviations

ACC	Anterior cingulate cortex
DLPC	Dorsolateral prefrontal cortex
FEF	Frontal eye fields
FSIQ	Full scale IQ
fMRI	Functional magnetic resonance imaging
FT	Children born full term (37 weeks+)
GA	Gestational age
IP	Posterior interposed nucleus
IVH	Intraventricular haemorrhage
IQR	Interquartile range
MST	Middle superior temporal visual area
MT	Middle temporal visual area
MT+	Human motion complex
MVN	Medial vestibular nucleus
NPH	Nucleus prepositus hypoglossi
NRTP	Nucleus reticularis tegmenti pontis
PN	Dorsal pontine nuclei
PPC	Posterior parietal cortex
PPRF	Paramedian pontine reticular formation
PT	Children born preterm (<32 completed weeks)
PVL	Periventricular leukomalacia
rCBF	Regional cerebral blood flow
ROP	Retinopathy of prematurity
SC	Superior colliculus
SEF	Supplementary eye fields
SI	Saccadic intrusion
SNpr	Substantia nigra pars reticulata
SOA	Supraoculomotor area
SRD	Specific reading difficulty
SWJ	Square wave jerk

CHAPTER 1: Introduction

1.1 Aims of the thesis

The aim of the research described in this thesis was to quantitatively investigate both monocular and binocular oculomotor control in preterm children in comparison with full term controls. The rationale for the study was the increased incidence of visual and ocular motility disorders that have been reported in children born preterm (preterms), which in addition to the incidence of cerebral lesions could give rise to compromised oculomotor function. Given the long developmental period of vergence and antisaccade control, I examined these areas of oculomotor performance longitudinally to see if preterms showed the expected refinement and improvement in control that occurs in full term children (full terms). I also investigated the preterms for the presence of any specific reading disability and for any association between reading difficulties and oculomotor or visual and binocular anomalies.

In order to provide some background to issues surrounding prematurity, the first chapter of the literature review explores the nature of medical problems associated with preterm birth, survival rates and the incidence of preterm birth. Very little, if any, quantitative research has been undertaken on oculomotor control in preterm children. To begin to understand why preterms may be at risk of oculomotor defects and why eye movement or visual problems could affect their reading ability, the rest of Chapter 1 discusses the variety of deficits that have been found in visual function and binocularity in this group. Further

explanation of why preterms are likely to suffer from oculomotor control deficits comes from the many brain lesions that can occur, discussed in Chapter 2. In addition to periventricular leukomalacia (PVL) and intraventricular haemorrhage (IVH), attention is also given to the more recent reports of lesions that may affect structures involved in oculomotor pathways and a review of oculomotor control in preterms is undertaken. Having discussed the brain lesions which may occur in preterms, Chapter 3 explores the pathways involved for saccades, antisaccades, smooth pursuit and vergence, the development of eye movement control and the type of oculomotor deficit that could be caused by various brain lesions. Finally, Chapter 4 reviews the variety of cognitive and behavioural problems and the specific reading disability that have been reported, and how the visual, binocular and oculomotor problems that may affect preterms, could contribute to reading difficulties.

1.2 Epidemiology of preterm birth

Very preterm infants or those with very low birth weight (VLBW) are commonly defined in the literature as those who were born with a gestational age (GA) of less than 32 weeks (Fily et al., 2006, Foulder-Hughes & Cooke, 2003, Nosarti et al., 2005, Stoelhorst et al., 2003), or with birth weights of less than 1500g respectively (Evensen et al., 2004, Finnstrom et al., 2003, Hellgren et al., 2005, Skranes et al., 2005). There are a number of major neonatal complications that may follow preterm birth. These include pulmonary complications of respiratory distress syndrome due to lung immaturity (Suresh & Soll, 2001) which leads to

chronic lung disease (bronchopulmonary dysplasia), and necrotising enterocolitis, an inflammatory disorder of the gastrointestinal tract that occurs 100 times more frequently in preterm than full term neonates (Wiswell et al., 1988). In addition there are brain lesions such as intraventricular haemorrhage originating in the micro-circulation of the germinal matrix and periventricular leukomalacia resulting in either focal periventricular necrosis and cyst formation or diffuse white matter injury (Volpe, 1998).

Advances in medical technology over the past 20 years have meant that greater numbers of preterm infants are surviving (Allen et al., 1993, Larroque et al., 2004). The improved survival rates have mainly been due to the introduction of interventions such as antenatal corticosteroids and exogenous pulmonary surfactant. Corticosteroids in the management of threatened preterm birth, aids fetal lung maturation and significantly reduces mortality and morbidity (Lamer, 2002). Exogenous pulmonary surfactant improves lung function and is used in the treatment or prophylaxis of respiratory distress syndrome. The introduction of surfactant has had a dramatic effect with a 40% reduction in mortality and a 50% reduction in pneumothorax in babies born with a GA of less than 30 weeks (Hennes et al., 1991). Survival rates of preterms are typically between 84%-90% by 28 weeks GA and at 93%-95% by 32 weeks GA (Larroque et al., 2004, Ward & Beachy, 2003). At GA's of 23-27 weeks there is a large variation in the reported estimates of survival, despite little variation in the birth period of the cohort and subsequent medical technology. This ranges from a survival rate of

0% (Lefebvre et al., 1996) to 19% (Kramer et al., 1997) at 23 weeks and 36% (WGVLBI, 1990) to 85% (Nicholl & Giles, 1991) at 27 weeks. There are likely to be a number of reasons for the variation between the studies. Factors such as sociodemographic characteristics of the cohort, uptake of interventions to improve survival, inclusion and classification of stillbirths and live births and definition of the cohort by geographical or hospital centre, may all contribute to variations in the survival rate. Despite improvements in neonatal care, preterm birth is still a major clinical problem, and in industrialized countries is responsible for 70% of neonatal mortality and 75% of neonatal morbidity (Challis et al., 2001). In addition to this, there is evidence that since the early 1980s, the incidence of preterm births has increased leading to preterm delivery rates of 11% in the USA and between 5% and 7% in Europe (Goldenberg, 2002). A recent study found that the proportion of preterm deliveries increased by 22% between 1995 and 2004, with an increase in spontaneous preterm deliveries in low risk primiparous women of 51% during this time period (Langhoff-Roos et al., 2006). Premature birth is therefore a major issue in perinatal care with long-lasting consequences for the infants and their future development. The following sections of this chapter will explore the consequences of prematurity on visual function and binocular single vision.

1.3 Visual development in preterms

Infants who are born preterm form a very heterogeneous group resulting from the degree of prematurity, and associated with this, the extent of any ocular and

cerebral anomalies. Whilst there appear to be many reasons why visual development may be adversely affected, it has also been suggested that, particularly in healthy preterms, additional extrauterine stimulation could accelerate visual development (Mactier et al., 1988). Both arguments will be reviewed.

Preterm infants are born at a time when the retina is very immature. Whilst the central retinal photoreceptors are present at 24 weeks GA, the outer segments are poorly formed (Provis et al., 1985). Retinal mitosis in the peripheral retina continues until 29 weeks with rods still developing at 40 weeks GA (Hollenberg & Spira, 1972). In order to have high resolution detailed vision the fovea must be mature, achieved by a total absence of rod photoreceptors. Migration of cones towards, and ganglion cells away from the foveal pit only occurs after 57 weeks post-conceptional age, and the fovea does not reach full maturity with adult foveal width and cone diameter until 4 years of age (Yuodelis & Hendrickson, 1986). Up to 28 weeks GA there is also reduced clarity of the ocular media, at which time there is regression of the secondary vitreous. The factors affecting the retina and ocular media render preterms more visually deprived at birth than a full term infant. Visual deprivation of a developing mammalian retina has been shown to reduce the responsiveness of inner retinal synapses (Tian & Copenhagen, 2001), indicating that development of the retina is dependent on activity, in the same way the visual cortex requires stimulation during the critical period. In addition to the immaturity of the retina, the lids of preterm infants are

fused until 25 weeks and were found to be closed during 55% of observation periods at 26 weeks, 93% of observation periods at 28 weeks and 60% at 34 weeks, with a mean of 74% (Robinson et al., 1989). The closed eyelids act as red filters only allowing long wavelength light to be transmitted to the retina. Neonatal closed lids transmit 50% more red light than adult eyelids (Robinson et al., 1991). The immature visual system of a preterm neonate is therefore subjected to highly anomalous visual input both in terms of the nature of the stimulation and the stage of development at which the input is received.

Other areas undergoing substantial and potentially vulnerable development are the optic nerves, lateral geniculate nuclei and visual cortex. During the second and third trimesters a large amount of axonal loss and remodelling occurs. Approximately 1.85 million optic nerve fibres are lost between the second and third trimester to reach adult levels of about 1 million, which occurs at the same time as segmentation of inputs to the different lateral geniculate layers (Rakic & Riley, 1983). Optic nerve myelination begins at about 32 weeks GA, is still incomplete at term and continues up to 2 years of age (Magoon & Robb, 1981). In the visual cortex, just before and after birth, there is a rapid increase in the number of synapses, reaching maximum density at about 8 months of age (Garey, 1984). After this time synapses are eliminated in response to physiological and behavioural changes in visual function to reach adult levels by about 11 years of age. The effect of abnormal early environmental stimulation of the visual cortex due to prematurity, has been studied in monkeys (Bourgeois et

al., 1989). They found that while prematurity did not affect the rate at which the synapses increased or the level of overproduction; the size, type and laminar distribution of the synapses was significantly different between preterm and full term animals. Visual experience therefore must influence the maturation of the visual cortex by strengthening, modifying or eliminating the synapses that have already been formed rather that changing the rate of synapse production.

Given the extent of development that occurs in the retina, optic nerve, lateral geniculate nucleus and visual cortex before and around birth and the exposure to anomalous visual experience, it is not surprising that the process of visual development is affected by disruption in the differentiation of retinal neurones, interference in the production of synapses or the normal elimination of synapses, and as a result of abnormal visual experience affecting maturation of the visual pathway.

An alternative viewpoint is that in a healthy preterm neonate, additional time in an extrauterine environment could cause accelerated visual development as a result of additional visual experience. A stimulating effect could arise from early activation of neuronal pathways that rely on visual experience to enhance their rate of maturation. Evidence from electroretinogram (ERG) responses however, indicated that preterm birth has no effect on the maturation rate (Birch et al., 1992, Leaf et al., 1996). Visually evoked potentionals (VEPs) have also been used to assess the extent of maturation. The results indicated that the visual

cortex may undergo accelerated maturation but the optic radiations showed no increase in the rate of myelination (Taylor et al., 1987). The use of VEPs to determine the presence of increased maturation would appear to have validity as correlation has been shown between improvements on the VEP and physical changes in the brain at post mortem. An example of this is the reduction in the latency of the P_{100} wave occurring at the same time as myelin formation (Magoon & Robb, 1981). Flash VEP experiments have also demonstrated increased maturation of the N1 waveform in preterms, indicating accelerated development of the visual cortex (Tsuneishi & Casaer, 2000). The latency of the flash VEP though was not reduced, in agreement with Taylor et al. (1987), indicating that there was no increase in the rate of myelination. Studies using pattern-reversal VEPs found the response was variable and did not consistently show accelerated maturation (Kos-Pietro et al., 1997, Roy et al., 1995). This could be attributable to the heterogeneity often present amongst preterm populations, with a wide variation in the GA's ranging from 24 to 36 weeks (Kos-Pietro et al., 1997). Perhaps only the most premature infants would show the effects of extrauterine stimulation. A recent study assessed a variety of measures of visual function (contrast sensitivity, grating acuity and vernier acuity) using the sweep visual evoked potential technique in preterms (24-32 weeks GA) free from IVH/PVL or ROP greater than stage II (Mirabella et al., 2006). There were no differences in the threshold performances on any measure of visual function between preterms and full terms, demonstrating that the preterms neither had impairment nor enhanced visual function. However, the strength of the neuronal signal was

statistically significantly higher in preterms for contrast sensitivity and vernier acuity (but not grating acuity) which could indicate accelerated visual cortical development of low spatial frequency mechanisms that are not related to the measures of threshold.

There still appears to be some debate as to whether preterm birth affects the development of the visual system in a beneficial or harmful manner. Further research is required to build on the findings of the most recent study (Mirabella et al., 2006), continuing with the use of quantitative measures of visual function such as grating acuity, contrast sensitivity and vernier acuity with the sweep VEP. This will provide a greater insight into the functional maturation, as it appears that specific areas of visual function may respond differently to the effect of extra visual experience. In addition to potential problems with the development of vision, preterm infants are also at risk of ocular and cerebral defects that can affect visual function directly.

1.4 Cause of visual deficit in preterms

The two main causes of severe visual impairment in preterms are cerebral visual impairment and retinopathy of prematurity.

1.4i Cerebral visual impairment

Vision in preterm infants may be affected by disorders of higher visual processing, known as cortical visual dysfunction or cerebral visual impairment (Dutton et al., 1996). This occurs because of damage to the optic radiations,

compromising input to the visual cortex, and may result from either PVL or IVH (Christiansen et al., 2002, Jacobson & Dutton, 2000). The severity of PVL is directly linked to the severity of the visual impairment. Severe PVL affecting the peritrigonal white matter with a large extent of calcarine atrophy has been shown to cause reduced grating acuity (Casteels et al., 1997). When using grating acuity to assess visual function, the results need to be evaluated carefully. Grating acuity does not require recognition of the stimulus and therefore assesses a different aspect of visual function than acuity assessed by optotypes. Some children who have achieved normal grating acuity have only been identified as having a deficit when later tested with optotypes (Jacobson et al., 1996). This study also demonstrated that children with PVL also have difficulties with the crowding phenomenon (difficulty resolving linear optotypes, but single optotypes of the same size can be identified).

In addition to problems with acuity, cerebral visual impairment is often associated with an impaired ability to process visual information, known as a visual cognitive disorder (Pike et al., 1994) and children with PVL often perform poorly in tasks involving spatial and visuoperceptual abilities (Skranes et al., 1997). Even children with PVL who have near normal acuity, may show difficulties with simultaneous perception, depth perception, recognising familiar faces, movement perception and orientation (Dutton et al., 1996). Cerebral visual impairment associated with PVL can therefore present as a much more complicated problem than simply a reduction in acuity. The deficits may

encompass visuo-spatial problems and could indicate an abnormality of the dorsal stream – the pathway between the occipital and parietal cortex (Fazzi et al., 2004) responsible for visually guided action.

1.4ii Retinopathy of prematurity

Retinopathy of prematurity (ROP) is a vaso-proliferative disorder that occurs in an immature retinal vascular system. The International Committee for the Classification of ROP has described zones of the retina (figure 1.1) to allow ROP to be classified according the extent of vascularisation (An International Committee for the Classification of Retinopathy of Prematurity, 2005).

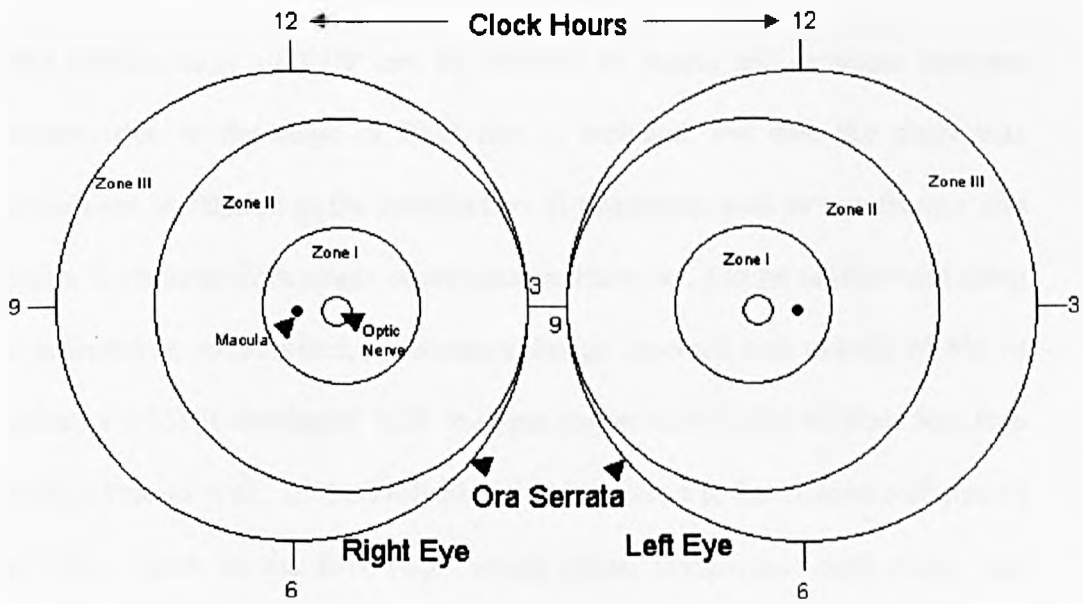


Figure 1.1 The International Classification of ROP Retinal Zones (An International Committee for the Classification of Retinopathy of Prematurity, 2005)

Progression of the disease is referred to in stages. Stage 1 is a demarcation line between vascular and avascular retina. In stage 2 the line becomes a ridge and projects into the vitreous. Stages 1 and 2 are mild ROP and usually resolve without requiring any treatment. Stage 3 involves extraretinal vascular proliferation with a ridge and neovascular tufts that can be found posterior to the ridge. In stage 4 scarring and fibrosis can occur when the neovascularization extends into the vitreous. This can cause traction on the retina, leading to a partial retinal detachment. Stage 5 is a total retinal detachment. 'Plus disease' refers to the presence of dilated and tortuous retinal vessels that may accompany any stage.

The epidemiology of ROP can be difficult to assess and compare between studies, due to the stage of ROP that is included, the date the study was undertaken in relation to the introduction of treatments such as cryotherapy and biases introduced from single centre studies. However, a large reliable trial using a prospective, randomized, multicentre design reported that overall 65.8% of infants (<1251g) developed ROP to some degree and 81.6% of those less than 1000g (Palmer et al., 1991). Probably of more interest is the incidence of stage 3 at 18%, which is the first stage where visual impairment may occur, and threshold ROP (stage where intervention is required) at 6%.

In order to determine the effect of ROP on visual function in low birth weights, a prospective study was undertaken which compared low birth weight children

with and without ROP (O'Connor et al., 2002a). This allowed determination of whether having low birth weight per se resulted in visual deficits, or whether it was attributable to the ROP. Children with severe ROP not surprisingly had the poorest acuity, but low birth weight children without ROP were also found to have a number of ophthalmic problems including altered eye growth resulting in myopia, reduced visual function and an increased risk of strabismus. Preterm birth or low birth weight would appear to cause increased risk of a number of visual and ocular deficits resulting from poor visual development, cerebral visual impairment or ROP, or any combination. The next section will explore the extent of ophthalmic morbidity in preterms via the commonly used measures of visual acuity, contrast sensitivity, strabismus, stereopsis, refractive errors and presence of nystagmus.

1.5 Ophthalmic morbidity in preterm children

Many studies have found ophthalmic impairments in preterm children, but most studies predate recent improvements that have been made in perinatal and neonatal care (Jacobson et al., 1996, Powls et al., 1997). Studies undertaken recently (Cooke et al., 2004, Larsson et al., 2005, O'Connor et al., 2002a, O'Connor et al., 2004) may more accurately reflect the extent of visual function deficits that now affect children born preterm. However, even the more recent studies are difficult to compare as they used different measures of visual acuity and contrast sensitivity and different inclusion criteria in terms of birth weight, GA and how low birth weight was defined.

1.5i Visual acuity and contrast sensitivity

Cooke et al. (2004) reported poor acuity in one or both eyes (defined as less than 6/9 Snellen) in 6.5% of preterms compared to only 1.4% of full term controls. O'Connor et al. (2002a) found some degree of binocular visual acuity loss (worse than 0.0 LogMAR) in up to 23.6% of preterms compared to 7.1% of controls. Though this appears to be a far higher proportion with impairment, actually only 3.5% of the cohort had moderately reduced acuity (worse than 0.3 LogMAR) and LogMAR is much more likely to identify deficits than Snellen. Both studies also found significantly reduced levels of contrast sensitivity in preterms. A median contrast sensitivity score (Cambridge Low Contrast Gratings) of 190 (left eye) and 210 (right eye) in preterms was found, compared to 250 (right eye and left eye) for full terms (Cooke et al., 2004). Though both studies found similar results, the tests used by O'Connor et al. (2004) and Cooke et al. (2004), the Pelli Robson and Cambridge Low Contrast Gratings respectively, only assess contrast sensitivity at one spatial frequency. Recently a study has been undertaken using the Vistech Contrast Sensitivity Test, which measures contrast sensitivity at five spatial frequencies ranging from 1.5 to 18 cycles per degree (Larsson et al., 2006). Children born prematurely had statistically lower contrast sensitivity at all levels of spatial frequency. In addition, when children with previous ROP and neurological complications were excluded, significant differences in contrast sensitivity were still present at 3, 6, 12, and 18 cycles per degree. This indicates that as well as ROP, preterm birth per se has a significant impact on contrast sensitivity.

1.5ii Strabismus and stereopsis

Preterm cohorts have been shown to have an increased prevalence of strabismus, and this has recently been reported to be at 13.6% compared to 1.4% of full terms (Cooke et al., 2004). The prevalence has varied between studies from 3.1% in six month old infants without ROP (Laws et al., 1992) to 57% in five year olds born at less than 28 weeks GA (Schalij-Delfos et al., 2000). None of these studies however, investigated the type of strabismus or analysed if any factors were independently associated with it, at an age when all types of strabismus would have presented. These issues have recently been addressed (O'Connor et al., 2002b) and the overall prevalence for a geographically defined cohort was found to be 19.3% compared to just 3.0% of full terms. The increased prevalence observed in this study is probably more representative of the preterm population as a whole, as the study by Cooke et al (2004) excluded children with major neurological insults, who were not attending mainstream school. O'Connor et al. (2002b) found that there was a fairly equal proportion of exotropia and esotropia in preterm children, but there was a relative increase in exotropia in preterms compared to full terms. The factors independently associated with strabismus were ROP, birth weight, cerebral palsy, anisometropia and refractive error.

Given the increased prevalence of strabismus, it is not surprising that studies have also found reduced levels of stereopsis in preterms. Recent studies have found a total absence of stereopsis in between 12% (Hard et al., 2000) and 17% (Cooke et al., 2004) of preterms. The proportion of preterms with normal

stereopsis was between 48% (Cooke et al., 2004) and 69% (Hard et al., 2000). The large discrepancy between the proportions with normal stereopsis is likely to be due to the use of different criteria, with either less than 120" TNO (Cooke et al., 2004) or less than 60" TNO (Hard et al., 2000) used to define an abnormality.

1.5iii Refractive errors

During normal development in full terms, infants typically have a degree of hypermetropia (Cook & Glasscock, 1951) that reduces with visual experience during emmetropisation. It has been observed however, that preterm children often develop myopia (Fledelius, 1995, Gordon & Donzis, 1986) which can be severe in preterms with significant ROP (Quinn et al., 1992). A study investigating a population based cohort at ten years of age found significant refractive errors in 29.6% of children born prematurely, compared to 7.8% born at full term (Larsson et al., 2003). Clinically significant myopia (-1D or more) was found in 7% of preterm (PT) and 2% of full term (FT) children. There were also differences between the groups for hypermetropia (3D or more; 4% of PT; 1% of FT) and astigmatism (1D or more; 21% of PT; 4% of FT). Preterm children treated with cryotherapy had the highest prevalence of refractive error (64%), but again prematurity per se is an important risk factor with a prevalence of refractive errors in 26% of preterms without ROP. A recent study also found preterms to have an increased prevalence of all types of refractive error and those with ROP had an increased risk of anisometropia by six-fold, though the risk of development of myopia, hypermetropia and astigmatism was not affected by the

presence of ROP (O'Connor et al., 2006). Whilst there was no increased risk of developing myopia for those with ROP, the severity of myopia was significantly associated with the severity of the ROP. The study also reported that the refractive state in preterms was relatively stable during the first 10 years of life with a shift towards myopia of 1 dioptre.

The reason for the development of myopia in preterm children is not fully understood. In preterms with ROP the dysfunctional retina may affect growth signals or disrupt the normal migration of photoreceptors from the fovea and subsequently compromise the process of emmetropisation (Lue et al., 1995). Other factors such as an increase in corneal curvature (Inagaki, 1986), axial elongation (Kent et al., 2000, Ziylan et al., 2006), decrease in the depth of the anterior chamber or increased refractive power of the lens (Choi et al., 2000), may also play a role either in isolation or in combination.

1.5iv Nystagmus

Nystagmus may be frequently present in congenital or early acquired visual impairment (Gelbart & Hoyt, 1988). The mechanism for the development of nystagmus is not clear but requires the presence of some vision and ability to fixate. In children with periventricular leukomalacia 84% had either manifest or latent nystagmus (Jacobson et al., 1998). A more recent study reported that 76% of preterms with PVL had horizontal manifest or latent nystagmus of different waveforms, most often jerk nystagmus (Jacobson et al., 2002). The reason for

nystagmus in PVL may be due to damage to the optic radiations causing trans-synaptic retrograde degeneration resulting in an anterior pathway lesion (Jacobson & Dutton, 2000). Although the proportion of children with nystagmus in these studies is high, this is by no means representative of preterm children as a whole. The children who presented with nystagmus represent those with moderate to marked impairments, with subnormal visual acuity, spastic diplegia and mild to moderate PVL. There do not appear to be reports in the literature on the prevalence of nystagmus in preterm children as a whole, both with and without PVL.

Nystagmus has also been reported in preterm children with intraventricular haemorrhage (Christiansen et al., 2002, O'Keefe et al., 2001). Nystagmus was present in between 5% (Christiansen et al., 2002) and 18% (O'Keefe et al., 2001) of preterms with all severities of intraventricular haemorrhage (IVH). For those with mild IVH, the proportion with nystagmus ranged from 0% (Christiansen et al., 2002) to 20% (O'Keefe et al., 2001) and in severe IVH from 16% (O'Keefe et al., 2001) to 46% (Christiansen et al., 2002). The discrepancy between the studies may be due to the fact that there were also large differences in other factors that could contribute to nystagmus, for example the proportion of preterms that had severe ROP.

1.6 Summary

Preterm children are a high risk group for a number of factors affecting long term visual and binocular outcome. Visual outcome may be impaired by disrupted visual development, cerebral visual impairment, retinopathy of prematurity, refractive errors and nystagmus. Preterms also have increased prevalence of strabismus which could lead to amblyopia, and reduced levels of stereopsis. The causes of the visual problems are complex and often multi-factorial. In addition to ocular problems, preterm children are also at risk from a variety of cerebral lesions, many of which could compromise oculomotor pathways and these will be addressed in the next chapter.

CHAPTER 2: Brain lesions in preterms

Preterms are at risk from a variety of cerebral lesions. This chapter will first explore the most commonly reported lesions of IVH and PVL. Attention will also be given to recent reports of other cerebral deficits that may affect oculomotor pathways, in areas such as the cerebellum, thalamus, caudate nucleus and overall cortical volume. In order to put the brain lesions into perspective an overview of brain anatomy will be provided, followed by explanation of how the anatomy of a preterm brain differs to that of an infant born full term.

2.1 Overview of brain anatomy

2.1i Cerebral topography

The brain consists of two hemispheres whose surface is furrowed by sulci and has intervening ridges known as gyri. The deepest are the lateral sulcus and central sulcus which roughly divide the hemisphere into frontal, parietal, occipital and temporal lobes. The outer surfaces of the hemispheres contain neurones with unmyelinated axons, whereas those in the more central regions contain myelin. The presence of the myelin sheath around the axons gives these regions of the brain a white appearance (termed white matter) as opposed to the grey matter of the outer surface which contains the neural cell bodies. The hemispheres are joined by a large band of white matter, the corpus callosum (figure 2.1). The corpus callosum is the largest of the commissures, linking matching areas on the left and right cerebral hemispheres. Minor commissures

include the anterior commissure connecting the anterior parts of the temporal lobe and the posterior commissure which lies directly in front of the pineal gland.

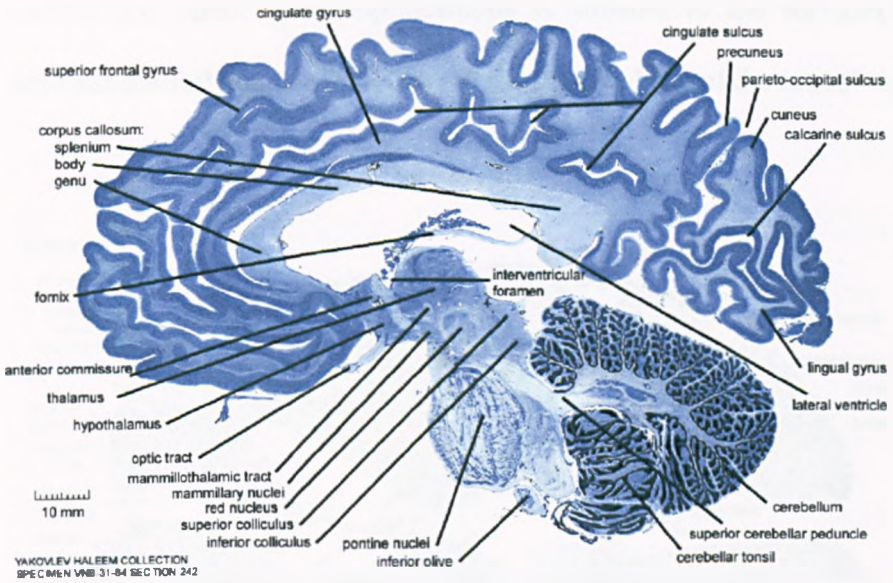


Figure 2.1 Sagittal section of the brain
(http://www.msu.edu/~brains/humanatlas/index.html)

The internal anatomy of the cerebrum (figure 2.2) contains the thalamus and hypothalamus (which form the diencephalon), caudate and lentiform nuclei (which form the basal ganglia with the sub-thalamic nucleus and substantia nigra), internal capsule, hippocampus, fornix and lateral and third ventricles. The two thalami face each other across the third ventricle and the upper surface of the thalamus is in contact with the head and body of the caudate nucleus. The tail of the caudate nucleus passes forward and below the thalamus. The thalamus is separated from the lentiform nucleus by the internal capsule, which contains

ascending fibres from the thalamus to the cortex and descending fibres from the cortex to the thalamus and brainstem. The lens shaped lentiform nucleus consists of the putamen and globus pallidus and the anterior ends of the putamen and caudate are fused. The hippocampus is situated in the temporal lobe and stretches the full length of the floor of the inferior horn of the lateral ventricle.

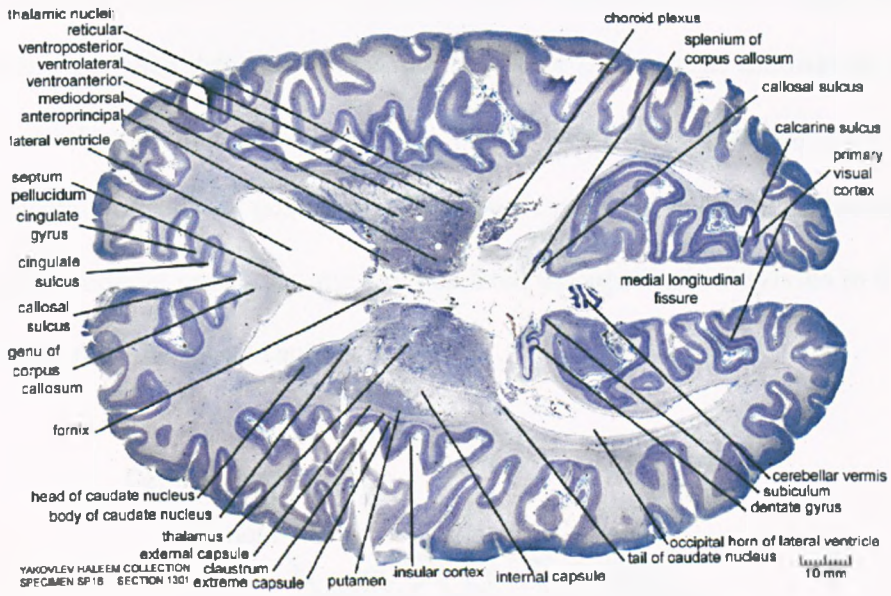


Figure 2.2 Horizontal section of the brain
(http://www.msu.edu/~brains/humanatlas/index.html)

During the development of the hippocampus, it retreats into the temporal lobe and leaves a tract of white matter, known as the fornix. The fornix contains fibres connecting the hippocampus to the septal nuclei and mammillary bodies (part of the limbic system).

2.1ii Ventricular system

The brain contains four ventricles: two lateral ventricles, the third and fourth ventricle (figure 2.3). Each ventricle contains a choroid plexus that produces cerebrospinal fluid. The two lateral ventricles are relatively large and C-shaped, roughly wrapping around the dorsal aspects of the basal ganglia. Each lateral ventricle extends into the frontal, temporal and occipital lobes via the frontal (anterior), temporal (inferior), and occipital (posterior) horns, respectively. The area where the three horns become confluent is known as the trigone. The third ventricle communicates with the lateral ventricles anteriorly and with the aqueduct of Sylvius posteriorly. The fourth ventricle is bound by the cerebellum and cerebellar peduncles and extends from the aqueduct of Sylvius to the obex at the start of the spinal canal.

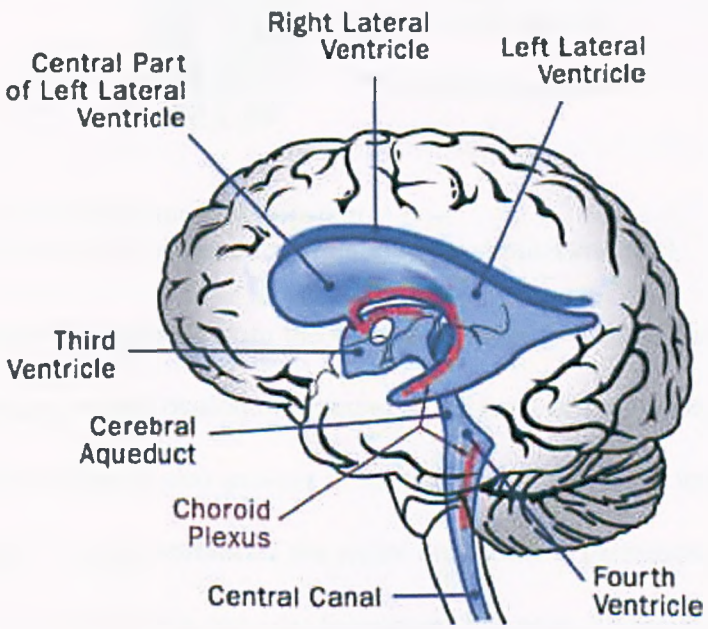


Figure 2.3 The ventricular system
(http://www.solarnavigator.net/human_brain.htm)

2.1iii Brainstem and cerebellum

The brainstem (figure 2.4) comprises of the midbrain, pons and medulla oblongata. The midbrain consists of the tectum, tegmentum and crus cerebri (cerebral peduncles). The tectum, made up of the superior and inferior colliculi, is located on the dorsal aspect, and the two large cerebral peduncles are situated on the ventral surface.

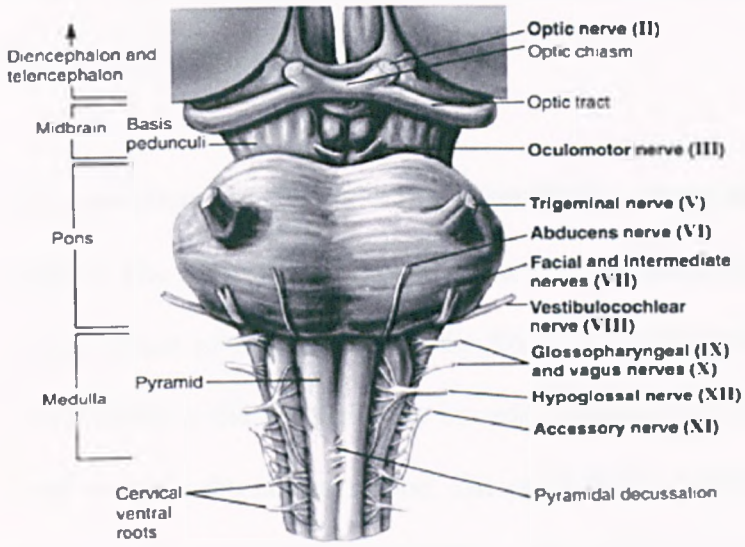


Figure 2.4 Ventral view of brainstem
(http://www.brainstemgenetics.org/about_the_brainstem.htm)

The tegmentum extends from the substantia nigra to the aqueduct of Sylvius and contains the red and oculomotor nuclei at the level of the superior colliculus. The trochlear nucleus is also present in the midbrain, but at the level of the inferior colliculus. The tegmentum of the entire brainstem is permeated by a network of neurones, known as the reticular formation. The pons is ventral to the cerebellum and contains a mass of transverse fibres. The cavity of the fourth ventricle is bordered laterally by the superior cerebellar peduncles above, which attach to the

midbrain and by the inferior cerebellar peduncles below, which attach to the medulla. The ventral area of the pons is the basilar region containing descending motor pathways and transverse fibres which enter the middle cerebellar peduncle. The abducens nucleus is located caudally in the pons beneath the fourth ventricle. The medulla oblongata is ventral to the cerebellum, caudal to the pons and rostral to the spinal cord. On the ventral aspect of the medulla are the pyramids, which contain the corticospinal fibres. Lateral to the pyramid is the olive and behind the olive is the inferior cerebellar peduncle.

The cerebellum is made up to two hemispheres, connected by the vermis in the midline. The oldest part of the cerebellum is the flocculonodular lobe, consisting of the nodule of the vermis and the flocculus in the hemisphere on each side. More recent is the anterior lobe bounded posteriorly by the fissure prima and most recent is the posterior lobe. The cerebellum contains four deep cerebellar nuclei in the centre of the cerebellum, embedded in the white matter. The four nuclei are known as the dentate, emboliform, globose and fastigial. The cortex of the cerebellum has three layers; from outer to inner layer, these are the molecular, Purkinje, and granular layers. The function of the cerebellar cortex is essentially to modulate information flowing through the deep nuclei.

2.2 Anatomy of the preterm brain

The appearance of the brain on MRI scan in preterm infants has been shown to be markedly different to that of full terms (Battin et al., 1998). In preterm infants

a structure known as the germinal matrix can be seen at the anterior and lateral margins of the lateral ventricles (figure 2.5). It is a structure that is most prominent between 24 and 34 weeks GA and has almost regressed by term. The germinal matrix tissue is abundant over the head of the caudate nucleus and can also be found in the periventricular region. It produces neurones and glial cells, which migrate to populate the cerebral cortex.

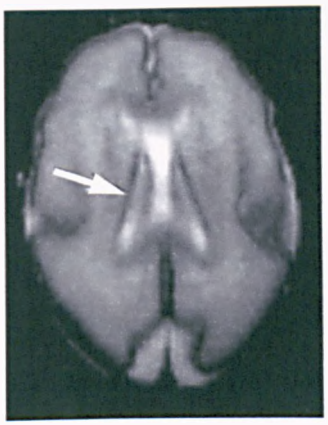


Figure 2.5 MRI showing the presence of the germinal matrix (indicated by the arrow) in preterm neonates (Battin et al., 1998)

The overall level of myelination is reduced compared to full terms. Myelination appears in the cerebellar peduncles by 25 weeks GA, followed by the inferior colliculi and ventrolateral nuclei of the thalamus. At 37-38 weeks myelination is evident in the posterior limb of the internal capsule. In terms of gyral development, very preterm infants show little cortical folding in some areas of the brain (figure 2.6). At 25 weeks the rim of the cortex is very simple with elementary sylvian and parieto-occipital fissures and rudimentary central, calcarine and cingulate sulci, but with increasing GA, sulcation and gyration increase in a systematic fashion.

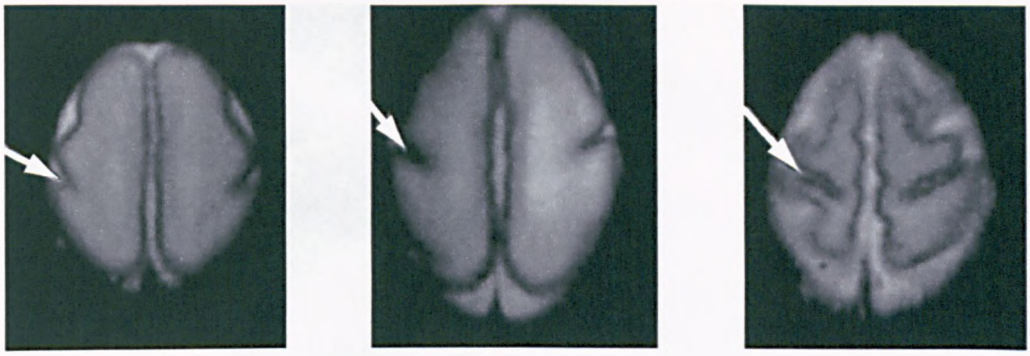


Figure 2.6 MRI showing extent of cortical folding in a preterm infant at 27, 29 and 32 weeks GA, the development of the central sulcus is indicated by the arrow (Battin et al., 1998)

Preterm children are at risk from a number of cerebral lesions, many of which could lead to problems of oculomotor control. The two most commonly reported brain lesions affecting preterms are periventricular leukomalacia and intraventricular haemorrhage. However, preterms are also at risk from lesions affecting the cerebellum, thalamus, caudate nucleus and overall cortical volume. The cause and prevalence of the brain problems will be discussed in each case.

2.3 Intraventricular haemorrhage

Preterm neonates have a limited ability to autoregulate cerebral blood flow. Impairment of autoregulation means that perfusion of the brain is dependent on systemic blood pressure. An abrupt increase in arterial pressure can lead to IVH either limited to the germinal matrix or rupturing into the lateral ventricles (figure 2.7).

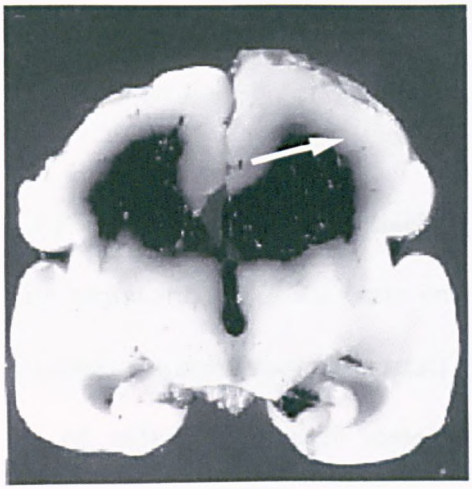


Figure 2.7 Severe IVH involving the whole of the lateral ventricles and extending into the parenchyma, as indicated by the arrow (Whitelaw, 2001)

The tissue is metabolically active with a thin microvasculature making it particularly susceptible to rupture. The grading system of IVH (Burstein et al., 1979) relies on the detection of blood in the subependymal germinal matrix and ventricles. Grade I refers to haemorrhage confined to the germinal matrix, Grade II involves the lateral ventricles but without hydrocephalus, Grade III has ventricular haemorrhage and associated hydrocephalus and Grade IV refers to a parenchymal haemorrhage. The proportion of very low birth weight infants (< 1500g) developing IVH in the early 1980s was between 35% and 50% (Philip et al., 1989). However, by the late 1990s this had reduced drastically to about 15% (Vohr et al., 2000). The reduction in incidence of haemorrhage may well reflect the advances in neonatal care occurring during this period. The main independent antenatal predictors of both IVH and PVL were found to be

spontaneous preterm delivery and reduced GA, with the risk of IVH increasing to 30% at 24 weeks GA (Vergani et al., 2004).

2.4 Periventricular leukomalacia

The major arteries of the brain encircle the cerebrum and send off penetrating branches towards (ventriculopetal) the lateral ventricles. There is also a further set of radially arranged vessels travelling out (ventriculofugal) from the ventricles which has long been thought to create a boundary zone or 'watershed', susceptible to a reduction in blood supply (Banker & Larroche, 1962). A reduction of systemic blood pressure in conjunction with impaired autoregulation of cerebral blood flow therefore leads to hypoxic-ischaemia affecting the vulnerable periventricular white matter. The resulting white matter atrophy, scar formation and occasional cysts are collectively known as periventricular leukomalacia. The location of the lesions is most commonly posterior, close to the trigone of the lateral ventricles, and less commonly anterior adjacent to the frontal horns (Shuman & Selednik, 1980). Later during infancy, the consequences of PVL can be identified; these include atrophic dilatation of the lateral ventricles, thinning of the corpus callosum and a reduction in the volume of white matter (figure 2.8). The incidence of bilateral cystic PVL in older studies has been estimated at between 3%-10% (De Vries et al., 1988, Trounce et al., 1986) and up to 32% if diffuse PVL is included (Olsen et al., 1997). Comparison of the studies can be difficult due to the use of different methods of classification, and different imaging techniques, such as ultrasound in the neonatal period or MRI later in life.

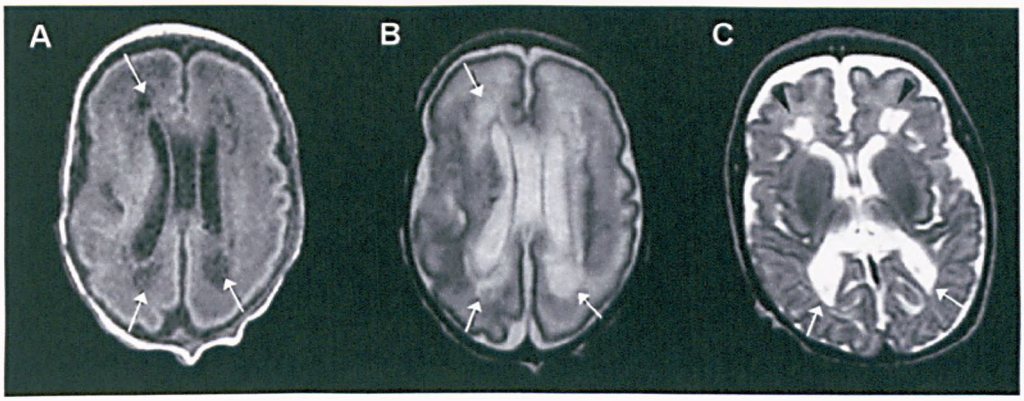


Figure 2.8 PVL in an infant born at 28 weeks GA, showing (A) cystic PVL within the white matter, (B) cystic lesions at high signal density and (C) loss of white matter in same infant at 40 weeks with squared off posterior horns of the lateral ventricles (Counsell et al., 2003), cystic lesions indicated by the arrow.

Ultrasound may not detect cases of diffuse PVL and has been shown to have a low sensitivity at only 26% (Inder et al., 2003a). Recent studies have shown that the incidence of cystic PVL has reduced throughout the 1990s and is now quite an uncommon finding, occurring in only 0.5% of surviving preterms (Hamrick et al., 2004). A recent study using MRI has found evidence of white matter injury in 64% of preterms less than 32 weeks GA (Inder et al., 2003b).

2.5 Lesions affecting the cerebellum in preterms

Although PVL and IVH have been largely reported in preterms, injury to the cerebellum has previously been far less recognised until the introduction of more sophisticated neuroimaging techniques in the 1990s (Mercuri et al., 1997). Cerebellar haemorrhage, which was clinically silent, has been detected in 6 out of 250 preterm children, using ultrasonography (Merrill et al., 1998). The

cerebellar haemorrhages could arise due to an increase in venous pressure, resulting from respiratory treatments such as full mask ventilation (Tuck & Ment, 1980) and extracorporeal membrane oxygenation (Evans et al., 1994b). The haemorrhages could also be related to impaired autoregulation of cerebral blood flow (Zernikow et al., 1994) or coagulopathy (Bulas et al., 1991). In addition to haemorrhage, the cerebellum may be at risk from infarction. Using MRI, 6 out of 73 preterm children were diagnosed with cerebellar infarction and a further 4 had cerebellar atrophy (Mercuri et al., 1997). The most commonly affected area was distribution from the posterior inferior cerebellar artery, with the vermis being involved in 4 of the 6 cases. Cerebellar infarction has also been investigated in preterms with cerebral palsy (Johnsen et al., 2002). All 13 children investigated had severe injury to the inferior cerebellar hemispheres and some injury to the vermis. The increased incidence of cerebellar lesions in this study is explained by the severity of other brain lesions suffered by the group, including severe cerebral palsy and microcephaly. Given the variety of lesions that may affect the cerebellum in preterms, studies have examined the cerebellar volume in relation to full term controls. There is agreement that the cerebellum has a significantly reduced volume in preterms and that the lateral lobes tend to be affected rather than the vermis (Allin et al., 2005, Argyropoulou et al., 2003). A reduction in volume has also been found to be correlated with a decrease in white matter and PVL (Shah et al., 2006a) and was associated with unilateral cerebral parenchymal injury with reduced cerebral volume (Limperopoulos et al., 2005b, Srinivasan et al., 2006). In addition to direct injury to the cerebellum, its volume

may also be affected by impaired development in preterms. A recent study found that the growth of the immature cerebellum is particularly rapid during late gestation and this accelerated growth is impeded by premature birth and other associated brain injuries (Limperopoulos et al., 2005a).

2.6 Evidence of lesions affecting the thalamus, caudate nucleus and overall cortical volume in preterms

PVL has been noted to cause lesions in parts of the brain other than the white matter (Paneth et al., 1990). MRI was therefore used to investigate the volume of the thalamus in 29 children with PVL (Lin et al., 2001). The ratio of thalamus to cerebellum was significantly smaller in preterms than controls, indicating a reduction in thalamic volume and that damage to the thalamus is associated with white matter injury. The use of the cerebellum as a reference could be subject to criticism though, as the authors considered the cerebellum to be normal in these children. However, as discussed previously, the cerebellum itself has been shown to have significantly reduced volume in preterms (Allin et al., 2005, Argyropoulou et al., 2003, Peterson et al., 2000). Lesions have also been found to affect the thalamus in preterms with spastic cerebral palsy (Yokochi, 1997). Analysis of MRI of 44 preterms showed thalamic lesions in 22 children, 19 of which were in the anterior part of the pulvinar. The children with thalamic lesions in areas other than the pulvinar showed the most severe motor and cognitive disabilities.

Evidence for injury to the caudate nucleus comes from a study that investigated 34 consecutive infants admitted to a neonatal intensive care unit with birth weights less than 1500g. Intracranial haemorrhage was found in 50% of the infants and in 41% of those, the haemorrhage affected the caudate nucleus (Reeder et al., 1982). Other vascular lesions in the form of an infarct of the lenticulostriate branch of the middle cerebral artery have also been found to cause damage in the region of the caudate nucleus (de Vries et al., 1997). Perhaps the most conclusive evidence though, comes from studies that have investigated the caudate volume (Abernethy et al., 2004, Abernethy et al., 2002, Nosarti et al., 2005). A study of 87 preterms, free from major neurological deficit and attending mainstream school were compared with 8 full terms. The volume of both caudate nuclei were significantly smaller in preterms compared to the full term controls (Abernethy et al., 2002). The caudate volume was also shown to be positively correlated with the level of IQ (Abernethy et al., 2004). The finding of reduced caudate volume is in agreement with Peterson et al. (2000) who also noted a significant reduction the volume of the putamen and globus pallidus. In addition to correlations with reduced IQ, decreased caudate volume in preterm adolescents has also been found to have some association with hyperactivity. Behavioural assessment of 72 adolescents born preterm and 50 age matched controls was undertaken using the Rutter Behavioural Scale to calculate a measure of hyperactivity. Preterm boys showed a significant negative correlation between hyperactivity and caudate volume, but for the left caudate only (Nosarti et al., 2005). The link between caudate volume and hyperactivity needs to be

viewed with caution though, given the association was not present for females and only present for the caudate on one side. The evidence for an association between reduced caudate volume and prematurity however, appears robust. Recent studies have investigated the presence of diffuse basal ganglia or thalamus hyperechogenicity in preterm infants (Leijser et al., 2004, Soghier et al., 2006). Hyperechogenicity is where structures appear white relative to the surrounding tissue. In terms of the basal ganglia and thalamus, this may indicate the presence of a variety of conditions including infection, haemorrhage, hypoxic-ischemic insult, infarction, calcifications or vascular lesions (Soghier et al., 2006). The latter study found basal ganglia and thalamus hyperechogenicity in 8% of preterms <34 weeks GA, and others have found the proportion to be even higher (26%) in preterms <32 weeks GA (Leijser et al., 2004).

As well as damage to specific brain structures, preterms may also be at risk from disruption of normal brain development. The brain of extremely preterm survivors only consists of a thin shell of tissue surrounding the cerebral ventricles, with virtually all of the normal cortical and sub-cortical architecture yet to be established. Subsequent physiological stress can seriously disrupt the maturational processes that develop this architecture (Rakic, 1988). To determine the potential consequences for preterms, cortical volumes were measured in comparison to full term controls. A significantly reduced cortical volume was found in preterms in the sensorimotor regions and premotor, parieto-occipital and subgenual cortices (Peterson et al., 2000). The volumes of the sensorimotor and midtemporal cortices were also positively associated with IQ scores. The finding

of cortical deficits concur with a recent study (Inder et al., 2005) that also found an overall reduction in cortical volume in preterms. The main predictors of cortical volume were GA and the presence of white matter injury. Preterms with significantly reduced cortical and deep nuclear grey matter volumes showed moderate to severe neurodevelopmental disability at 1 year of age. To determine if the brain abnormalities would persist as the children got older, a study examined the brain volume in preterms who were 15 years of age (Nosarti et al., 2002). Preterm subjects had significantly reduced whole brain and cortical grey matter volume (6.0% and 11.8%) and significantly increased lateral ventricles (42.0%). As expected, the results indicate that preterms have significant structural abnormalities that persist throughout childhood and into adolescence.

2.7 Summary

In Chapter 1 it was outlined how demonstrated that preterms are a high risk group for factors affecting visual and binocular outcome. This chapter has shown that in addition, preterms are at risk form a variety of cerebral lesions, not only PVL and IVH, but also lesions affecting the cerebellum, thalamus, caudate nucleus and overall cortical volume. Some of these lesions have only been identified recently with the aid of improving neuroimaging techniques and their true incidence may not yet be fully known. In terms of eye movement deficits, the significance of the brain lesions is that many of the structures are involved in the oculomotor pathways, and this will be discussed in the next chapter.

CHAPTER 3: Eye movements, neural pathways, development of eye movements and the consequences of brain lesions on oculomotor control

Preterm children are at risk from a number of cerebral lesions. To understand how these may affect the control of eye movements, this chapter will first review the nature and parameters of the different eye movement systems and then provide an overview of the neural control involved in each oculomotor pathway. Chapter 1 explored how visual function develops and how the maturation of various structures and pathways may be compromised due to premature birth. It follows that similar disruption could affect the maturation of eye movement pathways and so this chapter will also review the development of eye movement control. Finally, having reviewed the brain lesions affecting preterms in Chapter 2 and the eye movement pathways in this chapter, the type of oculomotor deficit that each brain lesion could cause will be examined, together with evidence of any eye movement deficits that have been found specifically in preterms.

3.1 Eye movement characteristics

3.1i Saccades

Saccades are rapid eye movements that direct the fovea from one point of fixation to another. They can be reflexive, where the eyes are directed to the appearance of a new stimulus or voluntary, where saccades are made on command, to the position of a remembered target (memory guided saccades) or in the opposite direction of a target (antisaccade). The parameters which might be

used to describe a saccade are its amplitude, duration, peak velocity and latency (figure 3.1). Additionally the saccade gain (amplitude of actual saccade / amplitude of desired saccade i.e. target amplitude) can be calculated, which is a measure of saccade accuracy. The duration and peak velocity of saccades can be characterised by their stereotypical relationship with respect to saccade amplitude (figure 3.2); this is known as the main sequence (Bahill et al., 1975). The relationship between peak velocity and amplitude is linear for saccades smaller than 20 degrees and linear for duration and amplitude between 1 and 50 degrees (Leigh & Zee, 2006).

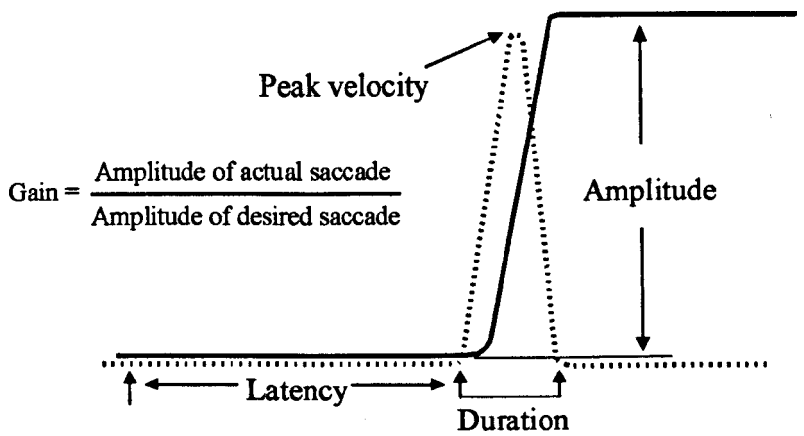


Figure 3.1 Saccade parameters

The peak velocity of a saccade can reach up to 700°/s for larger saccades, but is more typically between 200°/s and 400°/s. The duration of a saccade is very brief (often < 50ms), with a latency of around 200-250ms. As a result of the high velocity and short duration of saccades, there is no time for visual feedback to guide the eye to its final position. The eye movement is therefore pre-

programmed or ballistic and the saccade generating system cannot respond to subsequent changes in the target position during the course of the eye movement (Carpenter, 1988).

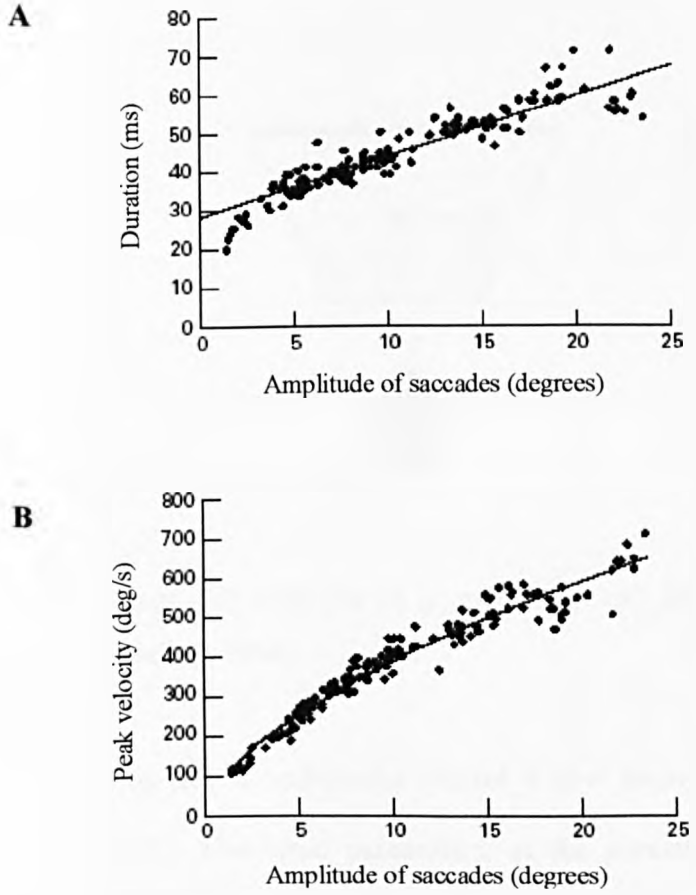


Figure 3.2 Main sequence relationship of (A) duration and (B) peak velocity (fitted with an exponential rather than a straight line in this example) against amplitude (Garbutt et al., 2001),

3.1ii Antisaccades

The ability to suppress reflexive responses and generate voluntary motor commands is crucial for everyday life. This allows a subject to direct attention to an area of choice rather than an area of stimulation, and is the basis of executive

function (Zelazo et al., 2004). Both of these abilities can be examined in an oculomotor task by presenting a visual stimulus at one position a given distance from fixation and asking the subject to look to the opposite side of fixation (figure 3.3).

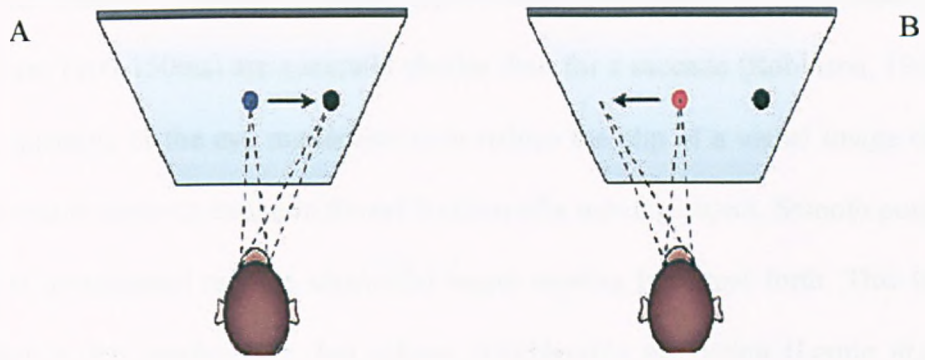


Figure 3.3 Example of a prosaccade (A) and an antisaccade (B) (Munoz & Everling, 2004)

This test of oculomotor control is now known as the antisaccade task (Hallett, 1978). The basic parameters, as for normal saccades, are latency, duration, velocity and amplitude, with the additional calculation of proportion of directional errors (prosaccades) and the time to correct the saccade. A deficit affecting the inhibition of reflexive responses will result in a high number of erroneous saccades towards the stimulus (prosaccades), whereas a deficit affecting the generation of voluntary movements will result in a low number of saccades to the opposite side (antisaccades). Error rates vary markedly with age and this will be addressed later in this chapter, when the development of eye

movement control is discussed. Antisaccade latencies have been found to be about 100ms longer than normal saccades (Van Gelder et al., 1997) and also have a reduced peak velocity by about 30% (Smit et al., 1987).

3.1iii Smooth pursuit

Smooth pursuit is a much slower type of eye movement (< 50°/s) and the latencies (100-150ms) are generally shorter than for a saccade (Robinson, 1965). The objective of the eye movement is to reduce the slip of a visual image over the fovea in order to maintain foveal fixation of a moving object. Smooth pursuit can be investigated using a sinusoidal target moving back and forth. This tests pursuit in the steady state, but allows considerable prediction (Leung et al., 2000). To determine how the smooth pursuit system responds to unpredictable target motion and assess latency, a target is used that steps in one direction before moving at constant velocity in the other direction i.e. step-ramp motion (Rashbass, 1961). If the target crosses the initial fixation point at approximately the same time as the latency of a saccade (200ms), the eye accelerates smoothly to acquire the target (Robinson & Fuchs, 2001). The initial 40ms of acceleration is relatively unaffected by the target velocity and serves only to start the eye in the correct direction. Acceleration between 40ms and 100ms depends on the target's velocity, position, movement direction and contrast (Lisberger et al., 1987). This is known as the end of the open loop period (figure 3.4) and from this point on visual feedback is available to close the loop (Wyatt & Pola, 1983). After the eye acquires the target, it moves at nearly target velocity resulting in

very little movement of the image on the retina. If retinal slip is eliminated completely by stabilising the target on the fovea, smooth pursuit still continues. This suggests that once pursuit movement has begun it is driven by a velocity memory and not a visual signal (Morris & Lisberger, 1987). The smooth pursuit system therefore requires predominantly visual signals to drive eye acceleration and oculomotor signals to control the maintenance of pursuit (Robinson & Fuchs, 2001).

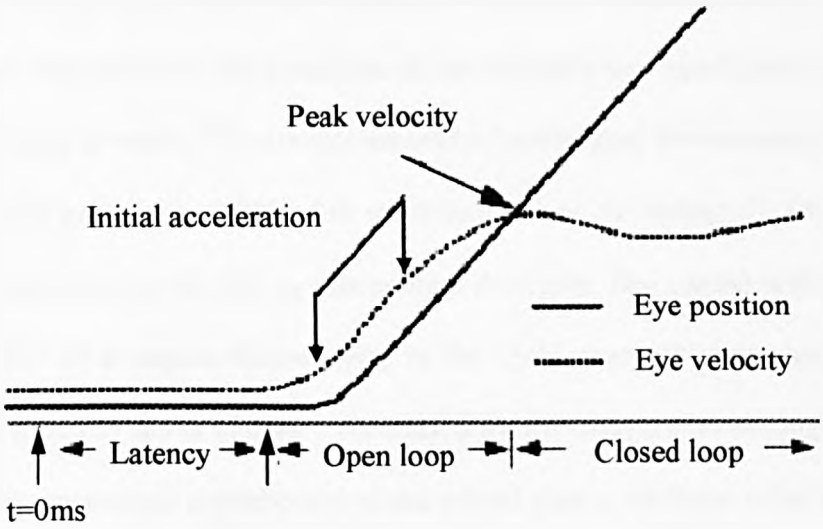


Figure 3.4 Smooth pursuit parameters

3.1iv Binocular co-ordination of saccades

Binocular co-ordination of saccades is essential in order to maintain binocular single vision with a fused image during eye movements. However, it has been found that horizontal saccades are asymmetric. At the end of a saccade the adducting eye drifts nasally in the direction of the antecedent saccade, while the abducting eye has a small zero-latency saccade in the opposite direction, known as dynamic overshoot (Kapoula et al., 1986). The eyes therefore tend to converge

at the end of a saccade and this is known as post-saccadic drift (Collewijn et al., 1988). This occurs as a result of mismatching between the pulse and step components of a saccade. In contrast to this, at the beginning of a saccade and at the offset, the eyes are divergent with a small amount of disconjugacy of less than 1 degree (Collewijn et al., 1988). Binocular co-ordination in children has been found to be particularly poor. Saccadic disconjugacy at the saccade offset was reported to be convergent between the age of 5-9 years and divergent for those between 11-13 years (Fioravanti et al., 1995). In addition to variation in the type of disconjugacy, the amplitude of disconjugacy was significantly larger than that found in adults. The average amount of convergent disconjugacy for the 5-9 year old group was 1.97°, with maximum values exceeding 4°. Binocular co-ordination improved with age (becoming divergent, like adults) with an average of 0.63° of divergent disconjugacy in the 11-13 year old group, similar to the level found in adults of 0.48°. The reason for the divergent disconjugacy may be due to mechanical asymmetries of the orbital plants. Stiffness when the left eye was rotated nasally was about 11% greater than when the same eye was rotated temporally (Collins et al., 1981). This of course does not explain why younger children showed disconjugacy in the opposite direction, and the reason for this is not clear. Perhaps it could be attributed to a greater immaturity of the vergence system in younger children. The reason for larger disconjugacy in children may be because the mechanism of disconjugate drift adaptation is poor and improves with age (Fioravanti et al., 1995). Also the asymmetry of the orbital mechanics is

large in young children and may exceed the range of disconjugate adaptation (Fioravanti et al., 1995).

3.1v Vergence

The function of the vergence system is to maintain foveal fixation as an object moves towards or away from the eyes. There are four components of vergence. The first is known as fusional or disparity-driven, and as the name suggests it is stimulated by retinal disparity i.e. where a visual stimulus is presented to both eyes but appears at slightly different locations on the retina. The second class known as accommodative, is induced by retinal blur of a near object and forms part of a near triad with accommodation and miosis of the pupil (Myers & Stark, 1990). The third type, referred to as tonic, represents the default level of convergence in total darkness resulting from the muscle tone of the medial recti and equates to about 3° of convergence (Glimcher, 1999). The final type, proximal vergence is generated by the sense of nearness of an object due to monocular depth cues, such as linear perspective (Enright, 1987).

The dynamics of vergence have not been as extensively studied as some of the other eye movement systems. There is also some discrepancy between the findings. Some studies (Alvarez et al., 2002, Yang et al., 2002, Krishnan et al., 1973) reported latencies to be longer for convergence (150ms, 250ms, 219ms) than divergence (130ms, 219ms, 198ms), whereas others (Hung et al., 1997, Semmlow & Wetzel, 1979) found longer latencies for divergence (182ms,

190ms) compared to convergence (161ms, 180ms). Also notable from the results is the large discrepancy between the magnitude of convergence and divergence latencies. Given the variability in vergence latency that has been reported between different studies, it is likely that this is the reason why there is such a lack of agreement as to whether convergence or divergence has the longer latency. Differences between the studies may have arisen due to the type of target used (variability of accommodative convergence), the method used to measure the eye movements, the age of the subjects (Yang et al., 2002) and the amount of vergence shift required (Alvarez et al., 2005). The peak velocity of vergence was also found to vary in relation to the amount of vergence exerted, and was greater for convergence than for divergence (Alvarez et al., 2005, Hung et al., 1997). The peak velocities also varied between subjects but most ranged from about 10-70 deg/s for convergence and 10-40 deg/s for divergence (figure 3.5).

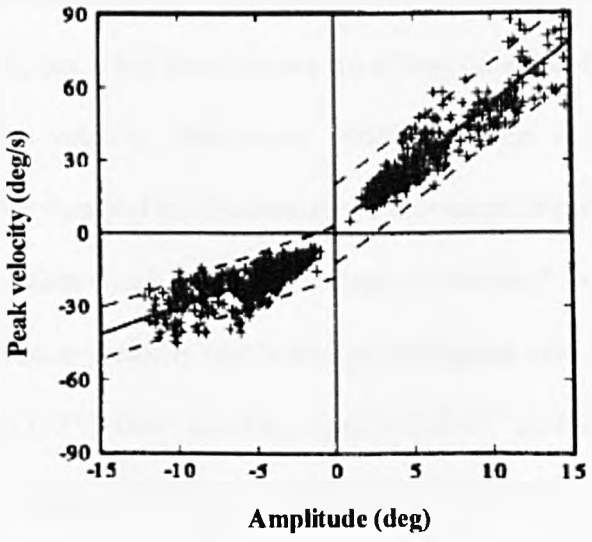


Figure 3.5 Main sequence of peak velocity vs. amplitude for vergence of 5 subjects (Hung et al., 1997)

This is vastly different however to a recent study that examined vergence in ten adults and fourteen children (Yang & Kapoula, 2004). The mean peak velocities for convergence (and divergence) were 228±105 deg/s (180±62 deg/s) in adults and 219±74 deg/s (160±58) in children. Other than differences in experimental techniques, it is not clear why there should be such large discrepancies between the studies, though there was clearly large variability between the subjects, especially for convergence as indicated by the large standard deviation. Given that there appears to be a large amount of variability within the group, it could be argued that a larger sample is required, in order to be confident that the mean can be generalised to the wider population.

3.1vi Fixation

The purpose of fixation is to maintain the image of a stationary object on the fovea. When an object is moving, image stability is achieved by smooth pursuit eye movements, but it has been known for a long time that fixation is not simply pursuit at zero velocity (Robinson, 1965). Fixation is therefore an active behaviour rather than just an absence of eye movement and involves inhibition of the saccadic system which will be discussed in section 3.2v. During fixation the eyes do not remain perfectly stable and physiological miniature eye movements such as tremor (15"/0.004° at 10'/s), drift (1-3'/0.05° at 4'/s) and microsaccades (5-10'/0.17° at mean 200°/s) have been noted to occur (Ditchburn & Ginsborg, 1953, Ratliff & Riggs, 1950, Steinman et al., 1973). The amplitude of tremor movements is extremely small and not correlated between the eyes, suggesting a

peripheral origin and the amplitude cannot be influenced voluntarily or by visual conditions (Carpenter, 1988). Drifts are larger and slower and again uncorrelated between the eyes. Microsaccades display the same main sequence properties in terms of velocity and amplitude as for larger saccades (Zuber & Stark, 1965). Microsaccades however, differ from larger saccades in that they have a greater amount of random variation both in direction and amplitude relative to the desired target though appear to be predominantly corrective in nature (Carpenter, 1988). More recently, there has been renewed interest in a further aspect of oculomotor behaviour - saccadic intrusions (Abadi et al., 2003). These are much larger than the other types of physiological eye movements and were found to be bilateral, conjugate and horizontal, with a mean amplitude of 0.6° and a range of 0.1°-4.1° (Abadi & Gowen, 2004).

3.1vii Summary of eye movement characteristics

The different types of eye movement can be characterised by their specific parameters, with notable differences in their velocities and latencies. Each has a specific function, with the general goal of directing or maintaining the fovea on the object of attention. The neural pathways subserving the different eye movement systems will now be explored.

3.2 Eye movements and their neural pathways

3.2i Saccades

A large body of literature, from lesion studies, human behavioural testing, functional neuroimaging, animal neurophysiology and detailed anatomical studies has identified numerous areas of the brain involved in controlling saccadic eye movements. The direction of a horizontal saccade is determined by the pattern of eye muscles activated. This is controlled by the paramedian pontine reticular formation (PPRF), located near the midline of the pons. The PPRF projects to the ipsilateral abducens nucleus and via the VI nerve to the lateral rectus muscle, but does not project to the contralateral medial rectus sub-division of the oculomotor nucleus (Buttner-Ennever & Henn, 1976). The medial rectus sub-nucleus is innervated by internuclear neurones, which originate from the abducens nucleus. The internuclear neurones cross the midline at the level of the abducens nucleus and ascend in the contralateral medial longitudinal fasciculus to provide the excitory input to the medial rectus sub-nucleus and via the III nerve to the medial rectus.

Single unit recordings in alert animals revealed three types of saccade related neurone (Fuchs et al., 1985). These are long-lead burst neurones, whose activity changes more that 100ms before saccade onset, premotor medium-lead burst neurones, which begin firing 8-12ms before the saccade and pause or tonic neurones, whose tonic discharge ceases before and during a saccade. Long-lead burst neurones are located in the PPRF and the nucleus reticularis tegmenti

pontis (Kaneko, 2006). The premotor burst neurones are located in PPRF rostral to the abducens nucleus (Horn et al., 1995) and the tonic neurones are located in the nucleus prepositus hypoglossi and the medial vestibular nuclei (Fukushima et al., 1992). Omnipause neurones are a special subgroup that are tonically active during fixation and suppressed during all saccades, irrespective of the direction. They receive input from the rostral pole of the superior colliculus (Gandhi & Keller, 1999), the area of the colliculus responsible for the inhibition of saccades. The omnipause neurones are situated in the pontine nucleus raphe interpositus and suppression of the omnipause neurones removes their inhibitory effect and allows activation of the burst neurones.

In order to overcome the drag of orbital tissues and start the eye moving there is a pulse of activity (phasic discharge) from the long-lead burst neurones which project to the premotor burst neurones (Scudder et al., 1996). This pulse determines the velocity of the saccade. The velocity signal is then mathematically integrated into the eye position command of the step (tonic discharge) which determines and maintains the eye position by a change in firing rate of the tonic neurones (figure 3.6). The conversion of the velocity command to the position command of the step is achieved by the oculomotor neural integrator, which encompasses a network of neurones but predominantly involves the nucleus prepositus hypoglossi and medial vestibular nuclei (Fukushima et al., 1992).

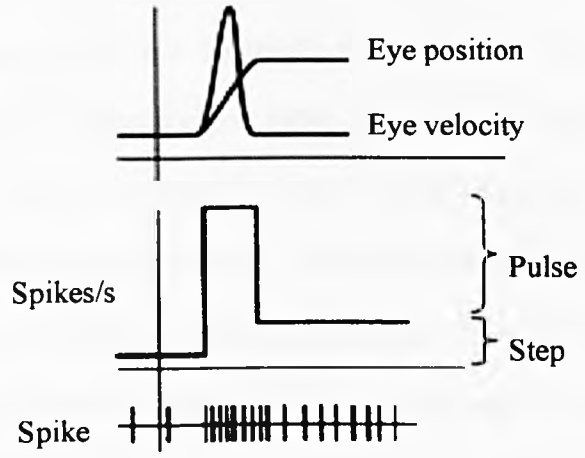
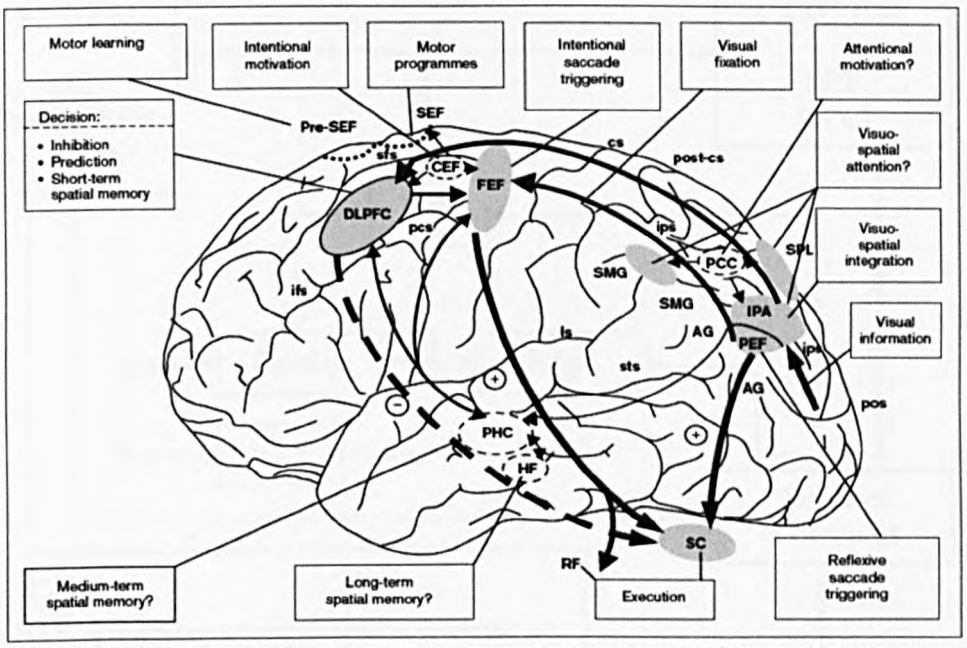


Figure 3.6 The pulse-step of a saccade

The superior colliculus (SC) located in the midbrain projects to the PPRF and provides the motor command to the burst neurones and also the inhibitory signal to the omnipause neurones to allow the saccade to be initiated. The caudal area of the SC stimulates saccades whilst the rostral area is inhibitory (Munoz & Wurtz, 1992). The dorsal layers of the SC form a visual area and receive visual inputs directly from the retina and visual cortex. The inputs are orderly and the visual field is mapped onto the surface of the SC (Cynader & Berman, 1972). The ventral, intermediate and deep layers of the SC form a motor area and contain a topographic motor map consisting of neurones that have a specific vector i.e. their stimulation produces a saccade with a particular direction and amplitude that is dependent of the site of stimulation rather than the strength of the stimulus or position of the eye (Robinson, 1972). The integrity of the SC is crucial for the production of reflexive saccades, including the production of express saccades (Pierrot-Deseilligny et al., 1991b). Express saccades are short latency (90-

140ms) reflexive visual saccades that are elicited when the fixation stimulus is removed early (i.e. before the target appears); this is known as the gap paradigm (Fischer & Ramsperger, 1984). The gap (the blank period between fixation offset and target appearance) causes the early release of a fixation mechanism for saccadic eye movements, resulting in a shorter initiation time. The SC is under the control of the substantia nigra pars reticulata (SNpr), which tonically inhibits the SC, except around the time of a saccade (Hikosaka et al., 2000). The SNpr stops firing when the caudate nucleus inhibits it at the time of a saccade. The frontal eye field activates the caudate and once the saccade has occurred, the SNpr resumes activity. In addition to the frontal eye field (FEF), several other cortical areas have found to contribute to the programming of saccades (figure 3.7). These include the supplementary eye field (SEF) in the upper part of the paracentral sulcus (Grosbras et al., 1999), the pre-SEF, located just anterior to the SEF and the parietal eye field, which lies in the intraparietal sulcus (Perry & Zeki, 2000).

Other areas involved in programming saccades are the dorsolateral prefrontal cortex (DLPC), on the dorsolateral surface of the frontal lobe, anterior to the FEF and the posterior parietal cortex (PPC). Frontal and parietal areas project directly to the superior colliculus and also indirectly through the basal ganglia. The superior colliculus therefore gets three different supranuclear signals from the SNpr, FEF and PPC. The SNpr inhibits activity of the colliculus.



SEF, supplementary eye field; sfs, superior frontal sulcus; CEF, cingulate eye field; cs, central sulcus; DLPFC, dorsolateral prefrontal cortex; pcs, precentral sulcus; FEF, frontal eye field; ips, intraparietal sulcus; ifs, inferior frontal sulcus; SMG, supramarginal gyrus; PCC, posterior cingulate cortex; SPL, superior parietal lobule; IPA, intraparietal areas; ls, lateral sulcus; AG, angular gyrus; PEF, posterior eye field; sts, superior temporal sulcus; pos, parieto-occipital sulcus; PHC, parahippocampal cortex; HF, hippocampal formation; SC, superior colliculus; RF, reticular formations.

Figure 3.7 Areas of cerebral cortex that contribute to the generation of saccades. (Pierrot-Deseilligny et al., 2004)

The FEF excites the colliculus (command to fire) and the caudate nucleus thereby stopping the SNpr, thus eliminating the inhibition to the colliculus (allowing to fire). The PPC provides an attentional signal which may be accompanied by saccades; it is also involved in the programming of saccades to visual targets (Bisley & Goldberg, 2003). The projections that contribute to the generation of saccades are summarised in Figure 3.8.

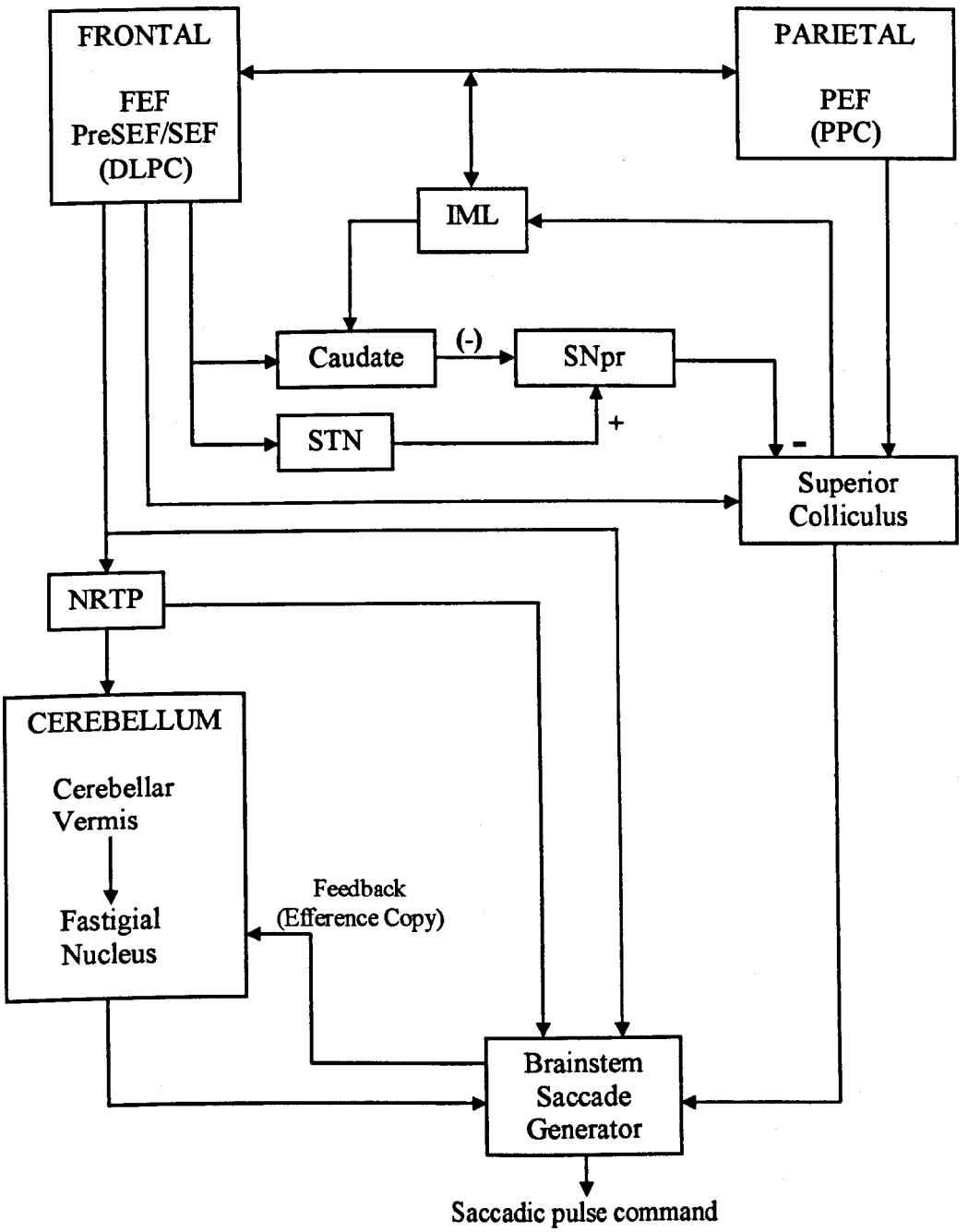


Figure 3.8 The major structures projecting to the brainstem saccade generator (PPRF), adapted from Leigh & Kennard (2004). FEF (frontal eye fields), SEF (supplementary eye fields), DLPC (dorsolateral prefrontal cortex), PEF (parietal eye fields), PPC (posterior parietal cortex), IML (Intramedullary lamina of thalamus), SNpr (substantia nigra pars reticulata), STN (subthalamic nucleus), NRTP (nucleus reticularis tegmenti pontis), + (stimulatory), – (inhibitory).

The cerebellum plays an important role in governing the accuracy of saccades, particularly the dorsal vermis (lobule VII) and the caudal part of the fastigial nucleus to which it projects (Robinson & Fuchs, 2001). The cerebellum receives a major projection from the cortical eye fields via the nucleus reticularis tegmenti pontis and also receives input from the PPRF (Voogd & Barmack, 2006). As well as receiving input from the dorsal vermis, the caudal part of the fastigial nucleus also receives a copy of the saccadic commands, which are relayed by the nucleus reticularis tegmenti pontis from the frontal eye fields and superior colliculus (Noda et al., 1990). It is postulated that the cerebellum governs saccade accuracy by monitoring motor commands, via copies of the commands themselves. These copies are referred to as the corollary discharge or efference copy signals, which terminate the saccade when it is calculated to have reached the target (Leigh & Kennard, 2004). Corollary discharge of all ocular motor signals are encoded by cell groups of the paramedian tracts, which project to the cerebellum along with other mossy fibre projections from the nucleus reticularis tegmenti pontis. The cerebellum may therefore receive the copy of the motor command signal from the superior colliculus via the nucleus reticularis tegmenti pontis and a feedback signal from the PPRF (Ohtsuka & Noda, 1992).

3.2ii Antisaccades

An antisaccade involves the inhibition of a reflexive prosaccade and the production of a voluntary saccade in the opposite direction. A number of

structures are believed to be involved in the generation of antisaccades (figure 3.9).

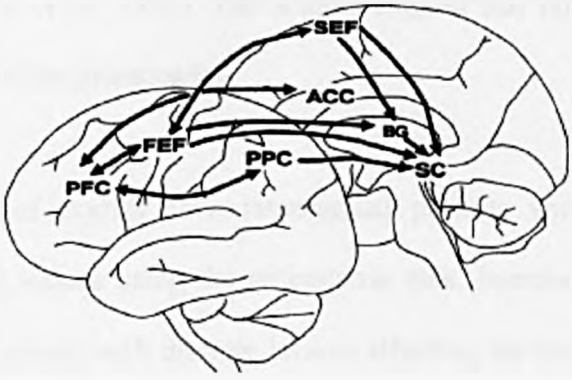


Figure 3.9 Structures thought to be involved in antisaccade generation, ACC = anterior cingulate cortex, BG = basal ganglia, PFC = prefrontal cortex, SC = superior colliculus (Everling & Fischer, 1998)

At a cortical level the DLPC seems to have an important role in the inhibition of unwanted saccades and therefore in the prevention of antisaccade directional errors (Pierrot-Deseilligny et al., 1991a). Patients with ischemic lesions of the mid DLPC have been found to have significantly higher antisaccade directional error rates (Ploner et al., 2005). Studies using functional neuroimaging techniques have found significantly increased regional cerebral blood flow (rCBF) during antisaccades in the area of the FEF, supplementary motor area, thalamus, putamen and superior parietal lobe (O'Driscoll et al., 1995). In contrast however, another study only found an increased rCBF in the areas of the anterior cingulate cortex (ACC) and PPC (Paus et al., 1993). The role of the FEF in antisaccades appears to be in the generation of the voluntary saccade (Dias & Segraves, 1999) and has been demonstrated in a patient with a discrete FEF lesion, not to be involved in the inhibition of reflexive saccades (Gaymard et al.,

1999). Single neurone activity in the SEF of monkeys showed this region to have a higher saccade related burst for antisaccades, compared with prosaccades (Schlag-Rey et al., 1997). The authors suggest that this discharge results in an inhibition of the prosaccades.

A variety of studies have investigated patients with different cortical and subcortical lesions using the antisaccade task. Increased error rates have been found in patients with discrete lesions affecting the superior colliculus (Pierrot-Deseilligny et al., 1991b), SNpr and caudate (Lasker et al., 1987, Rothlind et al., 1993) and frontal cortex (Guitton et al., 1985). Recently, investigation of the subcortical structures involved in antisaccade control revealed that patients with discrete lesions affecting either the basal ganglia or thalamus had normal antisaccade error rates, suggesting these structures may not be involved in the inhibition of reflexive saccades (Condy et al., 2004).

The extent of structures involved in the control of antisaccades is therefore yet to be determined, but may encompass numerous regions and it is likely that a distributed network of cortical and subcortical areas is involved. Recently, an event-related fMRI study found that the preparation of an antisaccade activated a large frontal and parietal network (Ford et al., 2005). The involvement of a large cortical network is also supported by the clinical finding that a variety of diffuse cortical lesions such as Alzheimer's disease (Currie et al., 1991), amyotrophic lateral sclerosis (Shaunak et al., 1995), acquired immunodeficiency syndrome (AIDS), dementia complex (Currie et al., 1988) and neuropsychological

consequences of old age (Klein et al., 2000) have all been found to cause increased antisaccade error rates.

3.2iii Smooth pursuit

Smooth pursuit also involves a number of cortical and subcortical structures and the major substrates and their connections are summarised in Figure 3.10. The visual signals for the generation of smooth pursuit reach the visual cortex (V1) via the lateral geniculate nucleus. The smooth pursuit system reacts to the motion of the target, rather than its position. Motion information is extracted in the striate cortex that recognises the moving target which then projects to the middle temporal (MT/V5) and middle superior temporal (MST) areas (Maunsell & van Essen, 1983). Studies in humans have shown that moving stimuli activate an area in the lateral occipito-temporal cortex which is thought to include the human homologues of macaque areas MT and MST, and has been referred to as the MT+ complex (Tootell et al., 1995, Watson et al., 1993). It has also been shown that like the macaque, the human area MT+ is also made up of two parts referred to as putative human areas pMT and pMST (Dukelow et al., 2001). The human motion complex therefore appears to be organised in a similar manner to the macaque. MST projects to the PPC where neurones have been found to be not only pursuit and therefore motion related, but also vision related (Kawano et al., 1984). The smooth pursuit related activity in the parietal lobe reflects attentional aspects rather than the precise neural coding of eye movements. MST also projects to the dorsal pontine nuclei (PN) and the FEF.

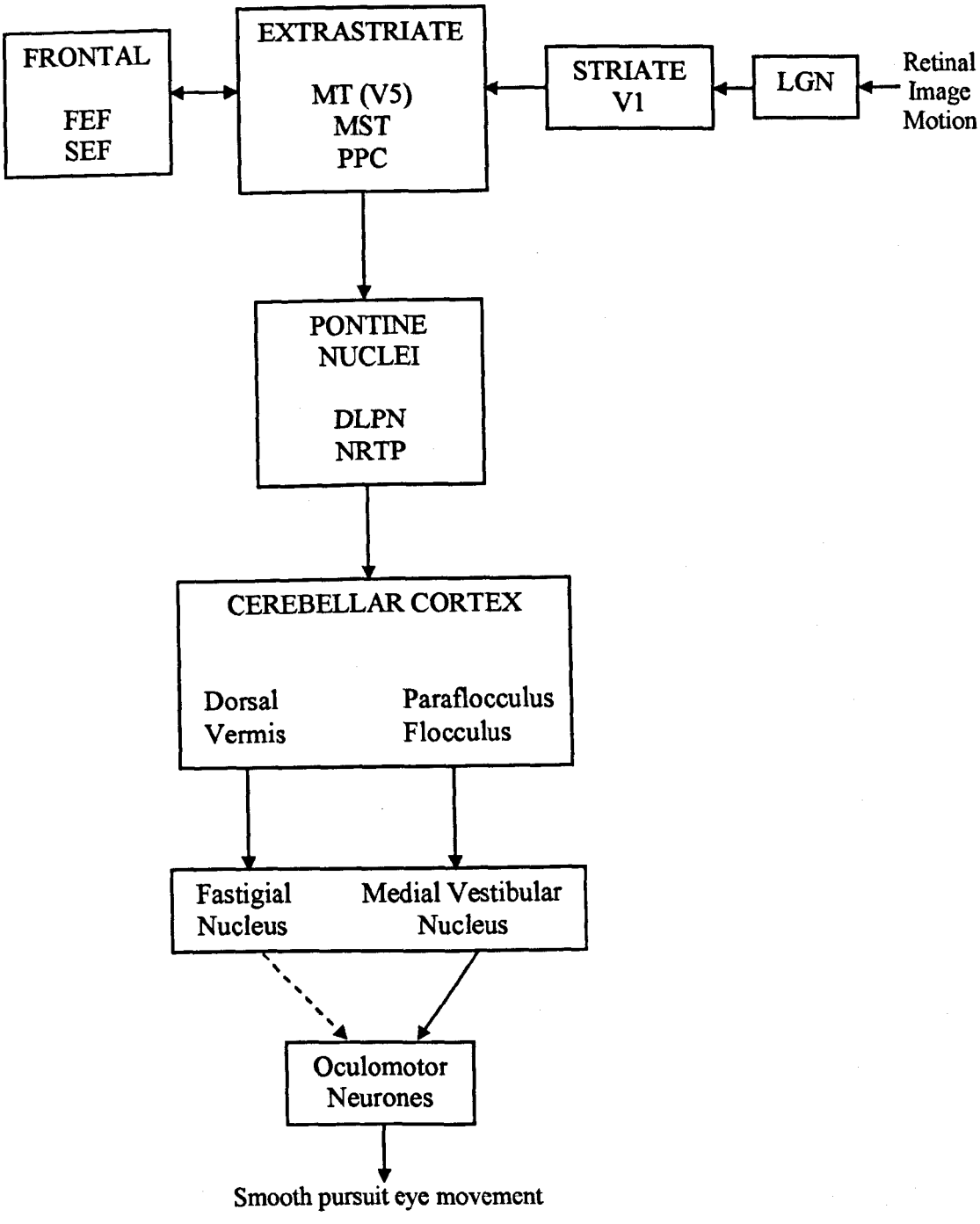


Figure 3.10 Hypothetical pathways for smooth pursuit adapted from Leigh & Zee (2006). LGN (lateral geniculate nucleus), MT (middle temporal visual area), MST (medial superior temporal visual area), PPC (posterior parietal cortex), FEF (frontal eye fields), SEF (supplementary eye fields), DLPN (dorsolateral pontine nuclei), NRTP (nucleus reticularis tegmenti pontis).

The FEF of the macaque has been shown to be separated into two functional sub-regions, one that lies on the rostral bank of the arcuate sulcus which controls saccades, and another that is located more posteriorly in the arcuate sulcus which controls pursuit (Gottlieb et al., 1993, Tian & Lynch, 1996). In humans, fMRI has also revealed distinct areas for pursuit and saccades in the FEF, with a smaller pursuit related region inferior and lateral to the saccade related region (Petit et al., 1997). Microstimulation experiments indicate that the FEFs are involved in setting the gain of the pursuit eye movement (Tanaka & Lisberger, 2002) and single-unit recordings suggest that this area is involved in predicting target trajectories (Fukushima et al., 2002) but it does not contribute to pursuit adaptation (Chou & Lisberger, 2004). Pursuit related neurones with predictive discharge have also been observed in the SEF (Missal & Heinen, 2004).

The dorsal pontine nuclei (PN) are the main efferents from the parieto-occipital and frontal areas concerned with smooth pursuit (Leichnetz, 2001). In contrast to early reports, signals related to pursuit have been observed not only from the dorsolateral area of the PN, but also in the medial and intermediate regions, together with saccade related activity throughout the dorsal PN (Dicke et al., 2004). The fact that both pursuit and saccade neurones are present in the PN and not kept separate, may be functionally significant, though this remains unclear. The concept that smooth pursuit and saccades are two distinct systems is currently being questioned, and it is suggested that both systems are closely linked, in some cases using the same neurones and sharing a similar functional

architecture (Krauzlis, 2005). The dorsal PN projects to the flocculus and paraflocculus and posterior vermis of the cerebellum (Leung et al., 2000). In addition these areas of the cerebellum also receive input from the nucleus reticularis tegmenti pontis (NRTP), located in the pons close to the midline and dorsal to the PN, which itself receives input from the lateral FEF and dorsomedial SEF (Shook et al., 1990, Stanton et al., 1988). Pursuit related neurones are more concentrated in the rostral part of the NRTP and microstimulation studies show they are strongly linked with eye acceleration, which may indicate that this area has a prominent role in pursuit initiation (Ono et al., 2005). In the cerebellum pursuit information from the flocculus and paraflocculus may be mainly required for the co-ordination of the vestibular reflexes with pursuit, for example tracking a target whilst moving the head (Rambold et al., 2002). Signals from the flocculus and paraflocculus reach ocular motor neurones via the vestibular nuclei (Roy & Cullen, 2003). In contrast to the primary role of the other pursuit area in the cerebellum, the posterior vermis, appears to be involved with the parametric adjustment of early open-loop pursuit (Thier & Ilg, 2005).

3.2iv Vergence

The neuronal structures involved in vergence appear to be the least well studied of all eye movements and the precise role of some cortical areas is yet to be identified. A summary of the identified and hypothesised neural pathways is summarised in Figure 3.11.

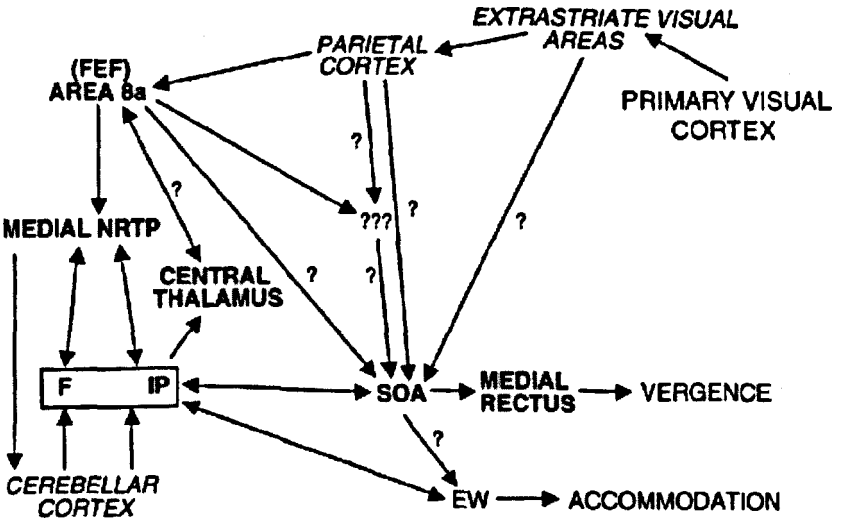


Figure 3.11 Neuronal pathways involved in the control of vergence eye movements. Areas known to contain cells related to vergence are indicated in bold lettering, those that appear from anatomical studies to contain vergence related cells are italicized and the areas that remain to be identified are indicated by question marks. EW = Edinger-Westphal nucleus, F = fastigial nucleus, IP = posterior interposed nucleus, SOA = supraoculomotor area, (Gamlin, 2002).

Neurones in the midbrain in the region known as the supraoculomotor area (SOA) and adjacent reticular formation around the oculomotor nucleus have been found to contain vergence related neurones that project to the oculomotor neurones (Zhang et al., 1991). There are three main types of neurone (Mays et al., 1986); those that discharge in relation to the vergence angle (tonic cells), to velocity (burst cells) and to both angle and velocity (burst-tonic cells). Vergence tonic cells increase their discharge 10ms-30ms before the eyes move, most in relation to the angle of convergence, but some in relation to divergence. Vergence burst cells discharge a burst of activity before and during vergence that

is correlated with the velocity of the vergence movement. Again there are both convergent and divergent burst neurones, with predominantly more of the convergent type. The vergence burst-tonic cells discharge a burst, related to the vergence velocity and a tonic firing rate related to the angle of vergence.

The vergence related neurones in the midbrain have connections with the deep cerebellar nuclei (Judge & Cumming, 1986, Zhang & Gamlin, 1998). Specifically neurones in the posterior interposed nucleus (IP) and fastigial nuclei were found to project to the SOA (May et al., 1992). Microstimulation in a localised region of the IP produced divergence eye movements with matching decreases in accommodation, due to phasic-tonic cells whose activity was modulated as a function of divergence and far accommodation (Zhang & Gamlin, 1998). The findings suggest that this region of the IP is involved in the control of the far response (divergence) whilst the fastigial nuclei appear to be involved in the near response (convergence). Single-unit recordings have also been made from the nucleus reticularis tegmenti pontis, which identified phasic-tonic cells that exhibited increases in their firing rate during the near response (Gamlin & Clarke, 1995). Many of these cells had a tonic firing rate that increased as a function of increases in convergence and accommodation. Also equal numbers of phasic-tonic cells were encountered in the NRTP that showed increase in activity during the far response. In a similar manner to saccades, the vergence system must provide positional information in order to maintain vergence at the end of the eye movement. For saccades this is achieved by mathematical integration of

the prior velocity command by the neural integrator. Models have shown that an integrator for vergence is also likely to exist (Krishnan & Stark, 1983) and electrophysiological evidence suggests that the NRTP makes a major contribution to the vergence integrator (Gamlin, 2002).

The two main stimuli for vergence are retinal blur and disparity (Judge, 1991). Some neurones in the primary visual cortex respond to disparate inputs from each eye (Trotter et al., 2004) and this has been reinforced by studies in humans where repetitive magnetic stimulation of the occipital cortex resulted in impaired stereopsis (Takayama & Sugishita, 1994). Neurones of the posterior parietal cortex have also been shown to be modulated in response to retinal disparity and additionally in response to the vergence angle i.e. target distance (Genovesio & Ferraina, 2004). The parietal cortex in turn projects to the frontal cortex (Petrides & Pandya, 1984, Thiebaut de Schotten et al., 2005), which has been shown to have vergence related neurones (Gamlin & Yoon, 2000). Other areas important for stereopsis, that are disparity sensitive, are the areas MT/V5 (DeAngelis & Newsome, 1999) and V3A in humans (Backus et al., 2001). The MST area has shown variable responses to disparity stimuli, but MST neurones have been found to encode signals necessary for generating the initial responses of vergence (Takemura et al., 2001).

Investigation of the frontal cortex revealed that an area in the prearcuate cortex, anterior to the saccade-related region of the FEF, contained neurones displaying

phasic activity that correlated with vergence eye movements (Gamlin & Yoon, 2000). The study also found that microstimulation at the site of these neurones, produced vergence eye movement. The authors conclude that the FEF in primates should be extended to cover this area, given that this region has now been shown to contain neurones connected with saccades, pursuit and vergence. Despite the advances made in understanding the role of the frontal cortex in vergence, little is known about the location and role of other cortical areas involved.

3.2v Fixation

The control of fixation and saccades are intertwined as discussed previously. This is reflected by the fact that disorders of fixation often manifest themselves as saccadic intrusions and square wave jerks (Shaffer et al., 2003). Fixation has been shown to be partly under the control of the rostral pole of the superior colliculus (SC), where a subset of neurones (fixation cells) discharge tonically during fixation of a target, so facilitating fixation and suppressing unwanted saccades (Munoz & Wurtz, 1992). The fixation neurones in the rostral SC project to the omnipause neurones which suppress the burst neurones in the PPRF (Bergeron & Guitton, 2001). It is thought that the fixation cells in the rostral SC may be part of the final common pathway from cortical fixation areas to the brainstem premotor circuitry (Munoz & Wurtz, 1993). In addition, saccade related cells in the caudal pole of the SC are under tonic inhibition by neurones in

the substantia nigra pars reticulata, which in turn is inhibited by the caudate nucleus (Hikosaka, 1989).

Research has shown that there are projections exclusively to the rostral fixation region of the SC, from the caudal fastigial nucleus and the posterior interposed nucleus of the cerebellum (May et al., 1990). There are also cortical projections to the SC from the FEF (Komatsu & Suzuki, 1985) and PPC (Lynch et al., 1985) and both the frontal cortex (Schlag et al., 1992) and PPC (Sakata et al., 1980) have neuronal activity that is modulated by active fixation. Additionally, a positron emission tomography (PET) study showed that during foveal fixation of a central target both the FEF and intraparietal sulcus were bilaterally activated (Petit et al., 1999). Contrary evidence was reported by another study however, that found that activity specifically in the region of the FEF was not modulated by fixation (Segraves & Goldberg, 1987). The PPC may therefore be more likely to be the region that has specific neurones involved in fixation, rather than the FEF. A clear role of the FEF in maintaining fixation though, seems to be in the suppression of unwanted saccades (Schlag-Rey et al., 1992) and it may act in an overall supervisory and inhibitive manner (Gooding et al., 1999).

3.3 Development of eye movements (saccades, pursuit, vergence and antisaccades)

As the preceding section demonstrates, the pathways involved in the various eye movement systems are very complex. It is not surprising therefore that precise

control of each system takes a considerable period to develop. This developmental period continues throughout childhood and possibly into adulthood for the more complex behaviours.

3.3i Development of saccades

Infants as young as four weeks old can reliably make saccades in the correct direction to targets with amplitudes of up to 40° (Salapatek et al., 1980). The reliability however, has been found to be much greater when target eccentricities are no more than 10°. For larger amplitudes saccades were hypometric, needing up to 5 saccades to reach the target. Though saccades can be generated in infancy, studies have shown that saccade control is refined throughout childhood (Klein & Foerster, 2001, Munoz et al., 1998, Yang et al., 2002). Munoz et al. (1998) investigated subjects from 5 to 79 years of age. The greatest amount of hypometria was observed among the youngest subjects age 5-8 years, in agreement with Salapatek et al. (1980). Analysis of the main sequence relationships showed that peak velocity was not influenced by age, but duration was shorter in young children, increasing and reaching adult levels by about 17 years of age. This result is probably explained by the hypometria found in children, which also improves with age and at a similar rate. The latency of saccades was significantly longer in young children (Klein & Foerster, 2001, Munoz et al., 1998, Yang et al., 2002). At age 4½-6 years latencies were 425ms, reducing to 280ms by 7-8 years and reaching adult levels of 225ms by 10-12 years (Yang et al., 2002). Further reductions in saccade latency occurred up to 18

years of age in other studies (Klein & Foerster, 2001, Munoz et al., 1998). The accuracy and latency of saccades therefore appears to develop throughout childhood and may only reach full maturity by 17-18 years.

3.3ii Development of antisaccades

The ability to perform antisaccades accurately is also poor in young children, but rapidly improves with age (figure 3.12). The directional error rate (number of errors/number of valid trials) was highest (around 50%) in the youngest age group tested (age 5-8 years), rapidly reducing to adult levels of 10% by 15-17 years (Munoz et al., 1998).

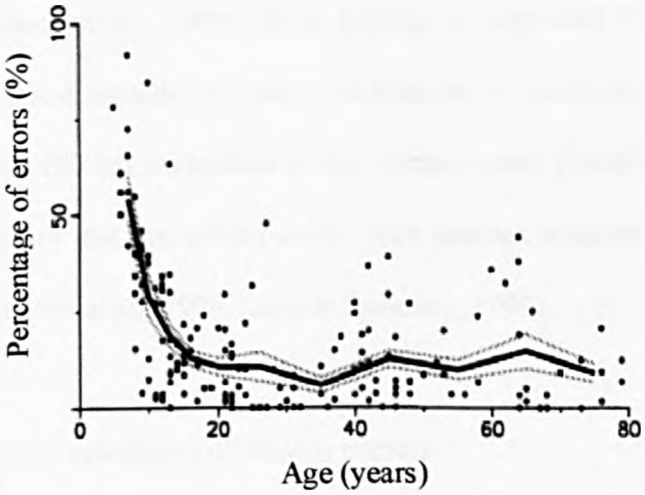


Figure 3.12 Antisaccade errors vs. age, solid line links the group means, dotted line represents the standard error of the mean (Munoz et al., 1998)

This is in agreement with other studies who also found the error rates were significantly negatively correlated with age during childhood (Fischer et al., 1997, Fukushima et al., 2000, Klein & Foerster, 2001). Fukushima et al. (2000)

found error rates of 58% at 7yrs, 45% at 8 yrs, 27% at 9 yrs and 18-20% at 10-12 years. Unfortunately no children were investigated over the age of 12 years, which would have allowed comparison of when adult error rates were reached. Fischer et al. (1997) found a similar trend, but with slightly higher error rates of 65% for children less than 10yrs, reducing to 22% by 15yrs and the lowest levels of 13% were reached by 20 years of age. Antisaccade control therefore appears to mature quite late, but has a rapid period of development between the ages of about 7 and 15 years. The high error rates may be attributable to poor control over visual fixation, which has to be maintained in order to suppress the prosaccade, and may reflect underdeveloped frontal and prefrontal cortices (Munoz et al., 1998). This finding is supported by the previous reports of increased saccade and vergence latencies in children, which were also attributed to insufficient maturation of the frontal cortex (Yang et al., 2002), and evidence showing that the frontal cortex only reaches maturity by about 15 years of age (Anokhin et al., 1996, Luna & Sweeney, 1999).

3.3iii Development of smooth pursuit

There is considerable disagreement as to the onset and accuracy of smooth pursuit in infants. Some authors have reported the presence of brief episodes of smooth pursuit in newborns and 4 week old infants (Kremenitzer et al., 1979, Roucoux et al., 1983). These studies however used large targets (visual angle up to 12°) and therefore may have elicited an optokinetic response (OKN), with the slow phase contributing to the following movement, rather than true smooth

pursuit. This is reinforced by the fact that binocular OKN has been readily elicited in infants, including newborns (Schor et al., 1983). Studies using smaller targets found smooth pursuit only to be present from 7 weeks of age, with saccades being used to track targets prior to this age (Aslin, 1981, Shea & Aslin, 1990). More recently however, again using smaller targets, segments of smooth pursuit were measured in the first 2 weeks of life, with a maximum velocity of 7.93 deg/s and maximum gain (eye velocity/target velocity) of 1.06 (Lengyel et al., 1998). It is likely that the difference in the findings is attributable to methodological differences, particularly the different techniques used to measure eye movements. The older studies used electro-oculography, while the more recent study used a video based corneal refection tracking system. Smooth pursuit gain has been shown to improve as the infant gets older. For 24 deg/s target velocities, gains were 0.6 at 1 month of age, 0.8 at 3 months and 1.0 for adults (Phillips et al., 1997). This study also found significantly longer latencies in infants of 512ms at 1 month of age, reducing to 381ms at 4 months, compared to 150ms for adults. It would be useful to conduct further research with children of different ages from infancy through to adults to assess the development of both pursuit initiation and maintenance in order to quantify when the improvements in performance are made, the rate of development and when adult levels are reached. A recent study (Salman et al., 2006) investigating pursuit in subjects from 8-19 years, also found that pursuit gain increased with age, and adult levels were only reached by about 17 years. The experiment used a predictive moving target (sinusoidal) and therefore did not investigate latency.

3.3iv Development of vergence

Vergence is necessary in order to maintain binocular fixation on targets whose distance and therefore depth vary. A consequence of poorly developed vergence is reflected in the normal occurrence of transient exotropia that has been reported in more than 40% of newborns (Archer et al., 1989, Sondhi et al., 1988). The early development of vergence has been investigated in infants aged between 17 and 120 days, using photographs and corneal reflections from magnified images to calculate the vergence angle (Hainline & Riddell, 1995). Infants as young as 20 days old were found to be able to control vergence sufficiently to maintain the image of the target on corresponding retinal areas, providing the basis for the later development of binocularity. The amount of misalignment between the eyes, due to poorly co-ordinated vergence, was on average 3.7° at 1 month, reducing to 2.8° at 2 months, 2.5° at 3 months and 2.1° at 4 months. Although the misalignments present for infants at 1 month of age showed co-ordination was less precise and the vergence control was more variable, the amplitudes were relatively small. Similar to the findings for saccades, vergence latencies have also been found to be significantly longer in children compared to adults (Yang et al., 2002). At age 4½-6 years latencies were 450ms, reducing to 300ms by 7-8 years and reaching adult levels of 230ms by 10-12 years (Yang et al., 2002). The authors postulate that the long developmental period for saccade and vergence latency is compatible with progressive maturation, especially of the frontal cortex.

3.4 The consequences of brain lesions on oculomotor control

Research into the oculomotor control of preterms is sparse and research using quantitative techniques, even more so. The research that has been undertaken, investigated preterms with specific brain lesions, namely IVH or PVL. The first two sections will therefore review studies that have investigated oculomotor control in children born preterm with these lesions. No oculomotor research has been directed to preterms with other brain lesions. The remaining sections will therefore explore the potential eye movement disorders that could result from deficits affecting the cerebellum, thalamus, caudate nucleus and cerebral cortex, using research involving subjects not necessarily born preterm.

3.4i Intraventricular haemorrhage

Recent studies have shown that IVH in preterms can cause increased risk of ocular motility problems. This is particularly so for high grade IVH (III or IV), where 73% have been found to have strabismus, compared to 14% of preterms with no or low grade (I or II) IVH (Christiansen et al., 2002). Other research however, has found a high incidence of strabismus (47%) even in low grade IVH (O'Keefe et al., 2001). The higher incidence in the latter study may be as a result of a much longer recruitment period, dating back to the 1980s when neonatal care was less advanced. A motility defect of limited abduction was found in 8% (Christiansen et al., 2002) and nystagmus was found in between 8% (Christiansen et al., 2002) and 18% (O'Keefe et al., 2001) of preterms with IVH. Saccades and smooth pursuit were not tested in either study. There have also

been reports of gaze palsy in children born preterm with IVH (Tamura & Hoyt, 1987). The children showed an absence of upgaze and esotropia, but did not have their eye movements investigated quantitatively.

3.4ii Periventricular leukomalacia (PVL)

PVL has a number of ocular consequences such as reduced visual function, nystagmus and strabismus (as discussed in Chapter 1). In addition, there have also been reports of some eye movement problems. Children with severe and moderate PVL have been noted to have 'significant abnormalities' with fixation and smooth pursuit, consisting of absence or difficulty with horizontal or vertical movements and also disengagement of central fixation to fixate a laterally placed target (Cioni et al., 1997). However, the methods of assessment (using a large piece of paper with back and white dots in front of the infant's face at a velocity of about 15°/s) were rudimentary and the problems found in the group with severe PVL may have been more related to difficulties resulting from poor acuity, rather than with the oculomotor system per se. Another study, using the Ober-2 infrared reflection technique, reported that many children exhibited inappropriate smooth pursuit, with several children having great difficulty following the target, and others performing smooth pursuit better in one direction than the other (Jacobson et al., 1998). In addition several children appeared unable to elicit voluntary saccades to the visually presented targets. Unfortunately no quantitative data were presented to support the descriptions of the eye movement deficits. The authors postulated that the eye movement deficits

may have arisen due to problems with motion perception (Dutton et al., 1996). Alternatively they suggest that the white matter lesions in PVL may injure the arcuate fibre bundles connecting the striate cortex with the middle temporal visual area (Tusa & Ungerleider, 1988), affecting the premotor commands for eye movement. More recently, Jacobson et al. (2002) have reported similar findings in another group of preterms with PVL. Many of the children who were tested had difficulties with both smooth pursuit and voluntary saccades, and had to use compensatory head movements, but again no quantitative data was presented. The control of eye movements has also been investigated in children with cerebral visual impairment following perinatal hypoxia, the majority (64%) of whom were preterm (Salati et al., 2002). Eye movements were videoed and given a numerical grading to indicate severe, mild or no impairment. Co-ordination of saccades was mildly impaired in 64% and severely impaired in 29%, and pursuit was mildly impaired in 75% and severely impaired in 21%. Fixation was mildly unstable in 63% and severely unstable in 21%. Though this study indicated a high level of impairment, the results need to be viewed with caution due the potential problems with the validity and reliability of the examination procedure, absence of quantitative data and difficulty generalising the findings to preterms. One study did explore smooth pursuit quantitatively using sinusoidal targets in six preterms, though their PVL status was not reported (Langaas et al., 1998). Children born prematurely had significantly lower gain (0.81) than full term age matched controls (1.03). Regression of gain against birth weight and GA were not significant, though the sample size was only small.

Given the predictive nature of the target presentation, no data could be gathered regarding pursuit latency and no other aspects of oculomotor control were examined. A recent study investigated eye movements in preterms between 23 and 33 weeks GA who had undergone MR imaging (Shah et al., 2006b). Oculomotor impairments were found in 31% of preterms (abnormalities of saccades in 10% and pursuit in 21%). The eye movements however, were only assessed qualitatively by direct observation using a toy as a fixation target and verbal commands to initiate the saccades. Therefore no data was presented about the control in relation to specific eye movement parameters, other than whether the eye movements were generally classed as normal or abnormal. Comparison with preterms infants without eye movement deficits revealed that those with oculomotor impairment had significantly smaller inferior occipital region brain volumes bilaterally, particularly for the cortical grey matter and the effect was greatest for those with abnormalities of saccades.

These studies demonstrate that oculomotor deficits may be present in children born prematurely, though most studies investigated preterms with specific disease and did not use quantitative techniques, limiting the conclusions which may be drawn.

3.4iii Cerebellar lesions

Oculomotor control has not been investigated in preterms with cerebellar lesions, but many studies have shown the important role of the cerebellum in the control of eye movements. A useful method of exploring the role of brain structures in oculomotor control is to examine the effect of lesions on eye movements. Saccade related neurones are present in the posterior lobe vermis and the caudal fastigial nucleus (Robinson & Fuchs, 2001). Disablement of the caudal fastigial nucleus has been found to cause variable, dysmetric saccades with reduced velocity (Robinson et al., 1993). A lesion of the vermis was also found to impair saccades causing both leftward and rightward saccades to be between 20% and 30% hypometric and saccade gains (saccade amplitude/target amplitude) to be twice as variable as normal (Barash et al., 1999). Smooth pursuit is also affected by lesions of the cerebellum. Bilateral ablation of the flocculus and the ventral paraflocculus caused a 33% reduction in horizontal smooth pursuit gain (Zee et al., 1981). The second cerebellar area involved with smooth pursuit is the posterior medial cerebellum, including the cerebellar vermis and the fastigial nuclei to which the vermal cells project (Noda & Fujikado, 1987). Surgical ablation of the vermis has been shown to cause a 30-40% reduction in pursuit gain (Keller, 1988). Cerebellar lesions may also cause problems with fixation. Square wave jerks, that are often variable and induced by a gaze shift, have been reported to have increased frequency in cerebellar disease (Rascol et al., 1991) This type of pathological square wave jerk therefore has different characteristics to the saccadic intrusions that have been commonly found in normal subjects

(Abadi & Gowen, 2004). Other fixation disorders such as opsoclonus (rapid, irregular, non-rhythmic movements of the eye in horizontal and vertical directions) have also been noted in a patient with gait ataxia and saccade dysmetria, suggestive of a cerebellar localization for the opsoclonus (Versino et al., 1999). In addition to conjugate eye movements, the cerebellum has also been shown to have a role in vergence and accommodation in experiments using monkeys (Zhang & Gamlin, 1998). Humans with cerebellar lesions have been found to have convergence excess or divergence failure (Leigh & Zee, 1991) and a patient with cerebellar signs was found to have difficulty with the release of accommodation (Kawasaki et al., 1993). It can be seen that cerebellar lesions may compromise a wide range of eye movements including saccades, smooth pursuit and vergence and may also affect the process of accommodation. The cerebellum therefore plays a key role in many areas of eye movement control and this could be important given the numerous reports of cerebellar lesions that have been found to occur in preterms (Allin et al., 2005, Argyropoulou et al., 2003, Limperopoulos et al., 2005a, Martin et al., 1976, Mercuri et al., 1997, Merrill et al., 1998).

3.4iv Thalamus, caudate nucleus and cerebral cortex

The thalamus is thought to play an important role in monitoring self-generated eye movements via the transmission of corollary discharge signals (Sommer & Wurtz, 2002). This is a feedback mechanism that is provided when a motor command is initiated (Sperry, 1950). In monkeys, a pathway for the corollary

discharge signals is thought to be present from the superior colliculus, via the medial dorsal nucleus of the thalamus to the frontal eye field (Sommer & Wurtz, 2004). Five patients with thalamic lesions were investigated to determine if lack of corollary discharge would cause saccade deficits (Bellebaum et al., 2005). The subjects demonstrated significant hypometria and asymmetry in comparison to controls. The asymmetry was thought to be attributable to lack of corollary discharge during sequences of saccades and the hypometria as a result of damage to fibres passing through the thalamus involved in saccade generation. Saccade generation has been investigated by inactivating the rostral portion of the ventrolateral nucleus and was found to cause increased latency of contralateral saccades, particularly those that were memory guided and initiated voluntarily during a fixed time period (Tanaka, 2006). Saccade latency (in reflexive saccades) has also been investigated in a group of patients with posterior thalamic lesions, using the gap paradigm (Rafal et al., 2004). The findings revealed no gap effect was present i.e. the latencies did not reduce (compared to the overlap trials) when the fixation target was removed prior to the appearance of the saccade target. This could reflect either a failure of the fixation neurones to be activated by the fixation target or a failure of the fixation neurones to be released from inhibition during the gap. The former is more likely, as the results showed that the latencies were similar for the controls and subjects for the gap trials. Disengagement of fixation for the subjects did therefore not reduce their latencies any further, as the fixation hold on the target was already weak. If this is the case, this type of lesion could also lead to antisaccade errors due to the

inability to suppress a reflexive prosaccade. Evidence against this comes from a recent study, where normal antisaccade error rates were found in a group of patients with isolated thalamic lesions (Condy et al., 2004). It is also possible that thalamic lesions could cause pursuit deficits. The activity of single thalamic neurones were recorded and showed directional modulation during pursuit eye movements (Tanaka, 2005). Most neurones discharged before or during initiation of pursuit and the firing rate was proportional to the target speed. When the moving target was briefly extinguished during maintenance of pursuit, the neurones continued to fire, indicating that they carried extra-retinal eye movement signals. The results suggest that the thalamus may also regulate and monitor pursuit eye movements.

To investigate the effects of a lesion involving the caudate nucleus, its activity in a monkey was suppressed using chemicals (Kori et al., 1995). Saccade latencies were found to increase and both the amplitude and velocity of the saccades reduced. This suggests that a lesion may reduce the inhibitory effect of the caudate nucleus on the substantia nigra pars reticulata, thereby causing suppression of the saccades. A caudate lesion may also have consequences for smooth pursuit, as recently dense projections have been found from the smooth pursuit subregion of the frontal eye fields to the head and body of the caudate (Cui et al., 2003). These findings indicate that the caudate nucleus may play an important role, not just for saccades, but also in the control of pursuit eye movements via feedback loops involving the basal ganglia and thalamus. The

role of the caudate in pursuit has also been reinforced by a recent positron emission tomography (PET) study. The results indicated that there was an increase in the regional cerebral blood flow to the caudate during pursuit (O'Driscoll et al., 2000).

In addition to lesions affecting the thalamus and caudate, preterms may also suffer from a reduced cortical volume. It is therefore worth considering the effect of cortical lesions on oculomotor control. The frontal cortex plays an important role in the control of voluntary saccades and in the inhibition of reflexive eye movements. Studies have shown that lesions affecting the frontal cortex, particularly the dorsolateral (Guitton et al., 1985) and mid-dorsolateral prefrontal cortex (Ploner et al., 2005) cause significantly increased antisaccade error rates. This is in contrast to lesions only affecting the frontal eye field, where antisaccade error rates were found to be normal (Rivaud et al., 1994). However, it is proposed that whilst the dorsolateral prefrontal cortex may be involved in the inhibition of unwanted reflexive saccades, the generation of the correct intentional antisaccade in the opposite direction to the target, may depend mainly upon the frontal eye fields (Pierrot-Deseilligny et al., 2005).

Prosaccades may also be affected by damage to the cortex. A recent study investigated 12 patients with frontal eye field lesions and 9 with lesions restricted to the parietal cortex (Machado & Rafal, 2004). Patients with frontal lesions had asymmetrically increased reflexive saccade latencies. Those with parietal lesions

had longer latencies than controls when making saccades following informative cues, consistent with the role of the parietal cortex in shifting the focus of attention (Corbetta et al., 1998). Asymmetrical hypometria in addition to increased saccade latencies have also been found in patients with lesions affecting the frontal eye fields (Rivaud et al., 1994) and posterior parietal cortex (Heide & Kompf, 1998). Cortical areas also have an important role in the control of smooth pursuit. Focal lesions affecting the occipitotemporal (Morrow & Sharpe, 1993), frontal (Morrow & Sharpe, 1990) and parietal (Thurston et al., 1988) cortex have been shown to cause ipsi-directional deficits of reduced pursuit gain. Patients with unilateral frontal cortex lesions exhibited problems with pursuit initiation, having increased latency in addition to reduced ipsi-directional gain (Morrow & Sharpe, 1995). Cortical lesions may therefore cause a wide range of oculomotor deficits affecting antisaccades, saccades and pursuit. Whether this also applies where the lesions are more subtle and diffuse, as might occur in preterms, remains to be seen.

3.5 Summary

The oculomotor control system is complex and involves numerous cortical and subcortical areas. Examination of the various eye movement systems provides a unique method to explore the behaviour and function of different brain structures. In addition to IVH and PVL, preterms are at risk from a variety of cerebral lesions affecting the cerebellum, caudate nucleus, thalamus and cortex. Preterms may as a consequence, suffer from eye movement disorders as a result

of damage to the pathways involving saccades, fixation, antisaccades, pursuit or vergence. Despite the likelihood of oculomotor deficits, these behaviours have yet to receive systematic quantitative investigation in preterms. Only one study was found that had used quantitative techniques and only pursuit maintenance was investigated in a small sample (Langaas et al., 1998). In addition to lesions directly affecting oculomotor control, certain aspects of oculomotor behaviour such as antisaccade performance and saccade/vergence latency have long developmental periods and may be susceptible to developmental delay. Similar disruption to development has been noted to affect visual function as discussed in Chapter 1. As well as oculomotor deficits, preterms may also suffer from cognitive problems including reading difficulties. This will be discussed in the next chapter together with any evidence that visual or eye movement defects may be associated with the reading problems.

CHAPTER 4: Cognitive and reading ability in preterm children and the association of visual and eye movement deficits

In addition to brain lesions and deficits of visual function, preterm children are also at greater risk from a number of cognitive and behavioural problems. This chapter will explore the nature of these deficits and the evidence that reading difficulties may occur as a specific disorder, in the presence of normal IQ. Finally, evidence that visual, binocular and oculomotor anomalies found in preterms may be associated with specific reading difficulties will be reviewed.

4.1 Cognitive and behavioural problems in children born preterm

Advances in neonatal care have increased the survival rate of preterm infants (Allen et al., 1993, Larroque et al., 2004), but concerns have been expressed that the survivors may be at risk from an increased neurodevelopmental morbidity. It has long been reported that preterm children suffer from multiple disabilities in the areas of cognitive ability and overall IQ (Klein et al., 1989, Marlow et al., 1993), spelling and speech (Luoma et al., 1998b), motor skills (Goyen et al., 1998, Luoma et al., 1998a), and attention deficit and hyperactivity (Hack et al., 1994, Horwood et al., 1998). It is important to note however, that the cognitive difficulties are not exclusively experienced by preterms with major disabilities (cerebral palsy, hydrocephalus, microcephaly, blindness and deafness), who only account for 14% of preterms (Whitfield et al., 1997). Typically it has been shown that 45% of preterm children have difficulty in one or more academic subjects (Marlow et al., 1993) and 27% require learning support (Horwood et al., 1998)

compared with only 19% and 9% respectively for full term controls. Many of the older studies however used hospital based cohorts (Goyen et al., 1998, Horwood et al., 1998, Klein et al., 1989, Luoma et al., 1998a, Luoma et al., 1998b, Marlow et al., 1993) which can introduce bias and cause difficulty in generalising the findings from research undertaken in specialised centres to the wider population (Vohr et al., 2004). In addition some studies (Goyen et al., 1998, Hack et al., 1994, Horwood et al., 1998, Klein et al., 1989, Marlow et al., 1993) used birth weight as an inclusion criteria, which can cause discrepancies in comparison to cohorts based on GA. Studies using low birth weight as the criteria will also include infants born at near term who were small for their GA and their morbidity may differ to that of preterms. More recently, studies using geographically defined cohorts and GA as the inclusion criteria, have also documented multiple cognitive, motor and developmental deficits in children born preterm (Cooke, 2005, Fily et al., 2006, Foulder-Hughes & Cooke, 2003, Salt & Redshaw, 2006). Foulder-Hughes and Cooke (2003) found motor impairment in 43% of preterms compared to 10% of full term controls using the Clinical Observations of Motor and Postural Skills assessment which provides an assessment of 'soft' neurological signs (deviations in motor, sensory and integrative functions that do not signify localized brain dysfunction, such as cranial nerve abnormalities, lateralized dysfunction or the presence of pathological reflexes; Breslau et al. 2000) and is thought to reflect cerebellar function (Wilson et al., 1992). Preterm children also had significantly more behavioural problems and reduced IQ. The mean full scale IQ was 89.4 in

preterms with 9% diagnosed as having attention deficit hyperactivity disorder, compared to 100.5 and 2% respectively for full term children (Foulder-Hughes & Cooke, 2003). Multiple regression showed that the IQ in preterms was independently significantly related to GA, patent ductus arteriosus (a condition where the ductus arteriosus, a blood vessel that allows blood to bypass the lungs in the fetus, fails to close after birth) and head circumference (Cooke, 2005). The deficits found in preterms also appear to persist through adolescence (O'Brien et al., 2004), where IQ was found to deteriorate slightly, and into adulthood where although the mean IQ was within the normal range, it was still one standard deviation below that of full term controls (Lefebvre et al., 2005). In addition to the cognitive and behavioural problems mentioned, preterms have also been found to have deficits in executive function (Anderson & Doyle, 2004, Taylor et al., 2004). Executive function refers to a collection of interrelated processes that are responsible for purposeful and goal directed behaviour and involves the elements of anticipation, goal selection, planning and organisation, initiation of activity, self-regulation, mental flexibility, deployment of attention, working memory and utilisation of feedback (Anderson, 2002). The executive function deficits found in preterm children tended to be global rather than in specific areas (Anderson & Doyle, 2004) and preterms showed slower development of executive function compared to full term controls (Taylor et al., 2004). Recently, young adults who were born preterm have been shown to have altered patterns of personality compared to full terms, with reduced extraversion and increased

neuroticism, which could predispose them to later psychiatric illness (Allin et al., 2006).

4.2 Reading difficulties in the presence of normal IQ

Many studies have reported that children born preterm have reading difficulties (Bowen et al., 2002, Horwood et al., 1998, Huddy et al., 2001, Saigal et al., 2003, Saigal et al., 2000), often in conjunction with other academic difficulties and a reduced IQ. Reading ability may be reduced as the consequence of global cognitive dysfunction, but there is evidence that some children born preterm have an IQ within the normal range yet still suffer from reading difficulties (Breslau et al., 2000, Grunau et al., 2002, Johnson & Breslau, 2000, Saigal et al., 1992, Taylor et al., 1995, Whitfield et al., 1997). These children have a specific reading difficulty (SRD), rather than a global learning deficit. Few studies have primarily investigated specific learning difficulties in preterms (Downie et al., 2003, Grunau et al., 2002, Johnson & Breslau, 2000, Saigal et al., 1992, Taylor et al., 1995) with the majority of studies quoting mean IQ scores for the entire preterm cohort, which prevents identification of individuals with a normal IQ ($\geq$85) and does not allow comparison with the reading data. The proportion of preterms with SRD has generally been quoted as being in the region of 23%-28% compared to 7% of full term controls (Grunau et al., 2002, Saigal et al., 1992) and ranging from 8.9% (Breslau et al., 2000) to 47% in a study where arithmetic and reading disorders were grouped together (Whitfield et al., 1997). The reason for such a low proportion of SLD being found by Breslau et al. (2000) is

probably because the inclusion criteria were extended to include birth weights of up to 2500g. Only 14% had birth weights less than 1500g and consequently the sample is likely to have contained children with less severe dysfunction than the other studies. The prevalence of SRD may also be affected by the method used for its identification. SRD is often defined on the basis of a discrepancy between the IQ and standardised reading scores. This could lead to underestimation of the true prevalence however as many preterms have an IQ at the lower end of the normal range and a reduction in reading ability may simply be viewed as being in line with their intelligence. A regression model can help to prevent the masking of SRD where the discrepancy criterion is decreased with IQ that is at the lower end of the normal range (Francis et al., 1990). An alternative method of defining SRD is by using the low achievement definition. This identifies children who obtain below average (<90) standardised reading scores (Taylor et al., 1995). This is a far simpler method of defining SRD and research has demonstrated that the two methods identify overlapping groups of children, showing similar ability profiles, with any differences being either small or not significant (Fletcher et al., 1994).

When considering the possibility of the effects of visual, binocular and oculomotor deficits on the reading ability in preterm children, it is important to examine the type of reading assessment that was used in the studies. Most of the research indicated that reading accuracy or single word reading was defective in line with the overall reading ability (Downie et al., 2003, Grunau et al., 2002,

Johnson & Breslau, 2000, Saigal et al., 1992, Taylor et al., 1995, Whitfield et al., 1997). Occasionally the reading accuracy was found to be satisfactory and only the reading comprehension impaired (Botting et al., 1998). If binocular or oculomotor deficits contribute to the reading difficulty the consequences would seem more likely to be miscues during the reading process, such as word omissions, reversals, substitutions, additions or mispronunciations, resulting in poor reading accuracy. Poor comprehension would obviously result from poor accuracy but defective comprehension in isolation would infer that the problem is more likely to be of cognitive origin rather than due to poor binocular or oculomotor control.

It is widely reported that reading difficulties are commonly experienced by preterm children. In addition, a sizeable proportion of these children have normal IQ ($\geq$85) and their reading difficulties cannot simply be attributed to an overall reduction of cognitive ability. Given the increased incidence of visual and binocular anomalies and potential for oculomotor deficits, it is possible that these areas could be associated with the reading difficulties experienced by preterms. Before evidence is reviewed for the role of ocular related deficits on reading ability, the next section will explore the eye movement and visual requirements for reading.

4.3 Eye movement, visual requirements and characteristics of normal reading

This section reviews the normal reading process, and includes some of the early work that was undertaken to identify the nature of eye movement control during reading. A basic visual requirement during reading is to form a clearly focused image of the text on the retina at the fovea. This is achieved by accommodation and pupil miosis with convergence to maintain foveal fixation. Foveal fixation is essential, in order to provide high resolution of the image with sufficient acuity. The saccadic system is also of crucial importance in reading. Forward saccades are made from left to right in order to visualise different words or elements of the words. Each forward saccade moves the eyes approximately eight characters (range 1 to 18) at a time (Tinker, 1939). In addition about 10% to 15% of saccades in reading are backward or regressive (Rayner, 1998). The purpose of these may be to recheck text for confirmation or they may occur as the result of confusion. In between these saccades are fixations; pauses which allow visual information to be extracted (an example of the eye movements that occur during reading can be seen in figure 4.1). The average fixation duration during reading is approximately 225msec (Tinker, 1951). The fixation duration and number of fixations may increase due to an increase in the complexity of the material or word ambiguity. Most words are only fixated once and some are not fixated at all, but despite this, fixation duration makes up the majority of the time taken to read. The percentage of total reading time taken up by the eye movements themselves is no greater than 10%, with an average of 7% (Tinker, 1939).

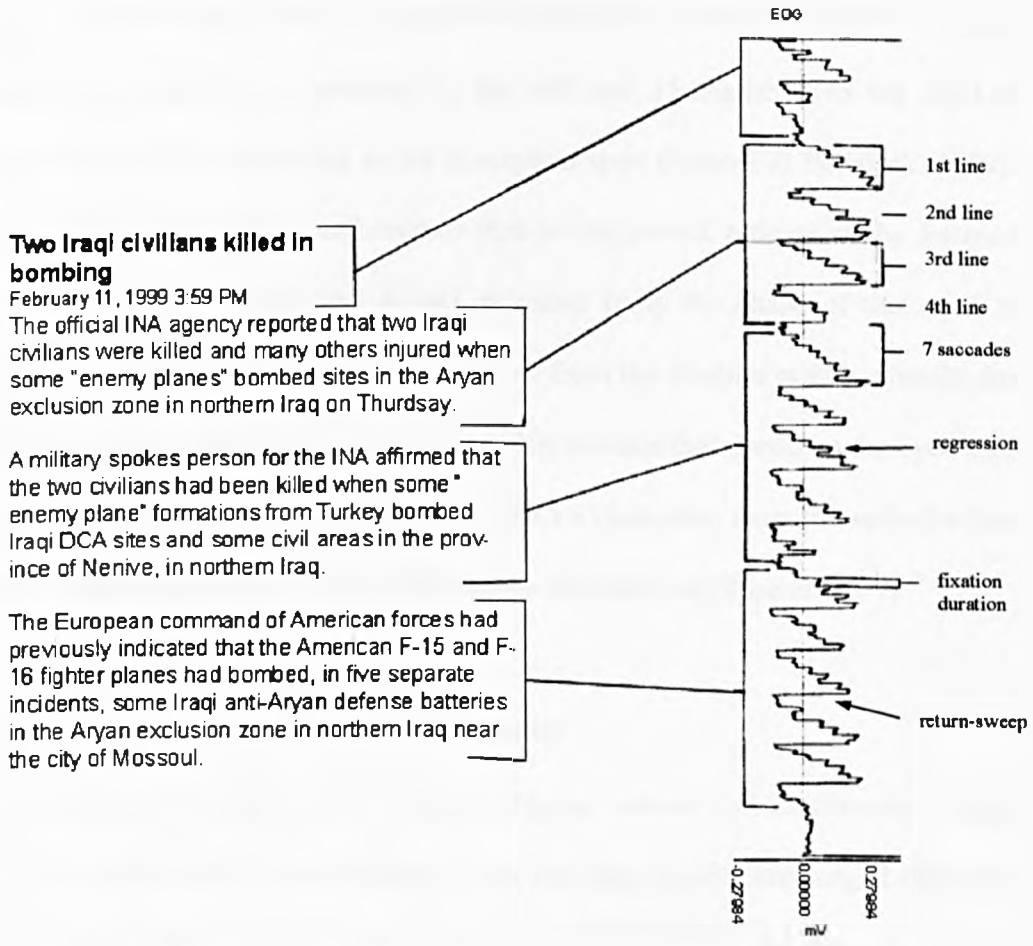


Figure 4.1 An example of an electro-oculography trace during the reading of a passage, showing saccades, fixations, regressions and the return-sweep (adapted from: http://www.biopac.com/bslprolessons/h14/h14.html).

As the length of the saccades can be as much as 18 characters and at the usual reading distance the fovea subtends a visual angle of one degree (only about $1^1/_2$ characters), some of the information must be extracted by the parafoveal area. It is thought that the fovea and area near to the parafovea are involved in semantic processing i.e. extracting information about the text, with areas further from the fovea functioning primarily to guide the saccade to the next fixation location

(Rayner & Bertera, 1979). The spatial direction from which information can be extracted (extending 4 characters to the left and 15 characters to the right of the fixation point) is known as the perceptual span (Rayner & Pollatsek, 1989). The clarity and degree of information that can be gained, reduces as the distance from the fixation point (and fovea) increases (only the shape of the word is obtained at a distance of 7 to 12 characters from the fixation point). Finally the return-sweep saccade is the large right to left saccade that occurs as the eyes near the end of a line, usually beginning at about 6 characters from the end of a line and finishing at about the sixth character on the next line (Rayner, 1977).

4.4 Oculomotor deficits and reading ability

In contrast to dyslexia, where the aetiological role of eye movements though proposed (Pavlidis, 1981, Pavlidis, 1985), has been heavily challenged (Black et al., 1984, Brown et al., 1983, De Luca et al., 1999, Ygge et al., 1993), neurological conditions such as multiple sclerosis, Huntington's chorea, choreatic syndrome, spinocerebellar degeneration, Wilson's disease, congenital oculomotor apraxia and Friedreich's ataxia, result in oculomotor deficits that can directly compromise reading ability (Ciuffreda & Tannen, 1995). The main research in this area is in the form of case reports, and these have been used in a study to document the effects of spinocerebellar disorders and Huntington's chorea (Pirozzolo & Rayner, 1979). A spinocerebellar disorder such as Friedreich's ataxia is an autosomal polyneuropathy, which leads to progressive dysfunction of the cerebellum, spinal cord and peripheral nerves. The cerebellar

lesion was found to cause saccadic intrusions and saccadic dysmetria, with large dynamic overshoots, leading to reading difficulties which the patient tried to overcome with the use of compensatory head movements (Ciuffreda et al., 1985, Pirozzolo & Rayner, 1979). Huntington's chorea is a familial progressive degenerative disorder causing gliosis and degeneration of the neurones in the caudate nucleus and putamen, resulting in a significant reduction in their volume (Aylward et al., 2003). The brain lesions cause dementia and involuntary motor movements. The oculomotor consequence of Huntington's chorea was found to be a significant reduction in peak saccadic velocity to about one third of normal, leading to reading difficulties (in the presence of normal IQ) and attempted compensatory head movements (Pirozzolo & Rayner, 1979).

Other case reports have been published for the conditions of Wallenberg's syndrome and multiple sclerosis. Wallenberg's syndrome is a complex of signs and symptoms such as vertigo, nausea, ataxia and cerebellar signs, caused by occlusion of the posterior inferior cerebellar artery. A patient examined with this condition showed gradual recovery over 2 years, with subsequent improvement in fixation and accuracy of eye movements during reading, correlating with an improvement in symptoms and reading ability (Tannen et al., 1989). Multiple sclerosis is a chronic disease affecting the central nervous system, with peak onset between 20 and 30 years and characterised by areas of demyelination. The demyelinating plaques can occur anywhere within the white matter, but commonly affect the optic nerves, brainstem, cerebellum and periventricular

region of the cerebral hemispheres (Pretorius & Quaghebeur, 2003). Symptoms and signs include numbness in the hands and feet, hemiparesis, blurred vision due to optic neuritis, double vision due to internuclear ophthalmoplegia and cerebellar signs. A patient with this condition was noted to have saccadic intrusions, present under all reading and non-reading conditions and complained of words moving and asthenopia (eye strain) during reading, compromising reading ability and causing visual disturbance (Ciuffreda et al., 1983). The saccadic intrusions occurred in brief bursts (1s-6s) with amplitudes of 2.0° to 8.5° (mean of 5°) and were more severe when the patient was fatigued. In addition to these studies, a collection of case reports has documented reading problems due to saccadic disorders resulting from choreatic syndrome (lesion affecting the basal ganglia causing involuntary motor movements) and ocular motor apraxia (defective initiation of voluntary and reflexive horizontal saccades) and in a variety of patients with disorders affecting fixation (Hartje, 1972). As well as disease, traumatic brain injury can also cause oculomotor deficits and subsequent reading difficulties. The prevalence of oculomotor problems in patients suffering from acquired brain injury ranges from 33% to 59% (Baker & Epstein, 1991, Lepore, 1995, Sabates et al., 1991, Schlageter et al., 1993, Van Stavern et al., 2001), with resultant oculomotor deficits including saccadic dysmetria, increased saccadic latency, reduced pursuit gain and ocular nerve palsies. The oculomotor deficits resulting from this type of brain injury have been found to cause reading problems, with symptoms during reading such

as loss of place, reduced speed (Hellerstein et al., 1995), and a sensation of visual motion (Ciuffreda et al., 2001).

To investigate any association between eye movement deficits and learning disorders, a study investigated reflexive saccades, antisaccades and pursuit (step-ramp stimulus) in 18 subjects with learning disorders and 22 controls (Fukushima et al., 2005). The authors hypothesised that as dyslexics and children with other learning disorders often show sensorimotor (auditory, visual and motor) abnormalities (Ramus, 2003) and disturbances of balance and gait (Moe-Nilssen et al., 2003), eye movement abnormalities may be present as a consequence of brain dysfunction or delayed development and be characteristic of learning disorders. The study found no differences between subjects with learning disorders and controls in the areas of reflexive saccade gain, peak velocity or latency, antisaccade errors or pursuit latency. However, subjects with learning difficulties had longer latencies for antisaccades, made more errors on memory-guided saccades and had significantly reduced open and closed loop pursuit gain. The results suggest that subjects with learning difficulties had some difficulties with the voluntary control of eye movements, but it is not clear, and the authors offered no explanation, as to why antisaccade error rates were not also elevated. Deficits occurring in both pursuit and saccade control may indicate a problem in the area of the FEF or SEF as both areas contain neurones involved in the programming of saccades and smooth pursuit (Krauzlis, 2005).

4.5 Visual and binocular anomalies and associated reading difficulty

Impaired eye movement control is not the only ocular cause of reading difficulties. Conditions causing deficits of binocularity and near vision, such as aniseikonia, anisometropia, large near heterophoria, poor fusional ability, reduced near point of convergence, intermittent strabismus, suppression and reduced accommodation, have also been shown to be related to and have a negative effect on reading ability (Ciuffreda & Tannen, 1995, Evans & Drasdo, 1990, Kapoor et al., 2002). Though this area has attracted some research, many of the studies are relatively old and further up to date research would be beneficial to enable firm conclusions to be drawn. In many cases it is not known if the ocular factors are associated or actually contribute to the reading difficulties.

Although intermittent strabismus has been found to be related to reading problems, constant strabismus with a total loss of binocular vision was not found to be associated with reading difficulty, though a positive correlation was found between fusional amplitude (in latent strabismus) and the reading score (Park & Burri, 1984). A more recent study using a case report documented similar findings (Rundstrom & Eperjesi, 1995). A 12 year old child with reading difficulties was found to have poor control of a convergence weakness exophoria, with no binocular convergence or stereopsis, and reduced accommodation and fusional reserves. Reading ability was reduced, with a reading age at four years below the subject's chronological age. The subject

complained that the words were jumbled, blurred and difficult to decipher and the symptoms improved monocularly. Treatment was given to improve the fusional reserves and binocular convergence, which improved over a few months together with the control of the exophoria, accommodation and stereopsis. Improvement in binocular control was matched by an improvement in reading fluency and accuracy and an increase in reading age to match the subject's chronological age. This suggests that the reading difficulties were caused by the binocular anomalies, though the conclusions would have had greater reliability if more than one subject had been studied and if a control group had been included for comparison. Another study found the amplitude of accommodation to be significantly reduced for children with reading difficulties (median 16D) compared to controls (median 20D), though no difference was present for accommodative facility (the ability to exert and relax accommodation repeatedly) (Evans et al., 1994a). However, given that only 3 dioptres of accommodation is required in order to read at the usual reading distance of a third of a metre, the difference found between the amplitudes is unlikely to be the main cause of the reading difficulties.

Visual anomalies have also been found to be associated with reading problems. A prospective study evaluated reading performance of 20 children with microtropia and amblyopia (Stifter et al., 2005). Microtropia is defined as a small angle strabismus, measuring less than 5° in which there is some demonstrable binocular vision (Lang, 1983). Children with microtropia and amblyopia had a

significantly slower reading rate and made more errors during reading than the controls. It is not clear though if this was attributable to the microtropia specifically, the amblyopia or a combination of both factors. Reading difficulties have arisen in other conditions where acuity has been affected, such as dense nuclear cataract (Stifter et al., 2004), age-related macula degeneration (Elliott et al., 2001) and anisometropic amblyopia (Osarovsky-Sasin et al., 2002). Patients with macular disease have also been shown to have significant impairment of fixation stability and although the control of fixation was not related to scotoma size, visual acuity or contrast sensitivity, there was a linear relationship with reading speed (Crossland et al., 2004). A reduced reading speed in patients with macular disease may therefore be partially attributed to poor control of fixation. Aniseikonia and anisometropia have also been linked with reading difficulties. Evidence from two older studies demonstrated a higher incidence (13%) of anisometropia in reading disabled subjects compared to controls (6%) and anisometropes on average had a reading age 1 year behind that of emmetropic controls (Eames, 1948, Eames, 1964). Aniseikonia has been investigated by artificially inducing the condition with lenses (Brod & Hamilton, 1973) and subjects with simulated aniseikonia made more reading errors than controls. The aniseikonia in this study was artificially and suddenly introduced however, and may not accurately represent subjects with the actual condition. Also it is not known if the reading difficulties would persist or whether there would be some adaptation over time and subsequent improvement in reading ability. The conclusions may therefore be unreliable, but it does provide an indicator of

potential difficulties, in the absence of any other research involving subjects with aniseikonia. Though further research is required, it can be seen that a variety of visual and binocular anomalies may contribute to reading difficulties.

4.6 Visual, binocular and eye movement disorders associated with reading difficulty in children born preterm

Research conducted in this area is extremely sparse (Downie et al., 2003, Ek et al., 2000). A study conducted by Ek et al. (2000) investigated reading ability in four preterm children who had PVL and associated visual impairment. All children had nystagmus, strabismus and clinical evidence of impaired motility. In addition all children had reading difficulties, though precise quantitative standardised reading scores were not quoted. Eye movements recorded by an infrared reflection technique (Ober-2) during fixation and reading indicated abnormalities in normal fixations, saccades, regressions and return sweeps. Also during reading the children made head movements in a saccadic fashion to try to assist their reading ability. Though this study has demonstrated reading difficulties in conjunction with eye movement abnormalities, it is difficult to draw any firm conclusions. The sample was clearly not representative of preterms. The children had numerous ocular and visual deficits which may have contributed to the reading difficulties. Also two of the four children in the sample had an abnormal IQ (< 85) and the reading difficulties may well be commensurate with an overall cognitive deficit, in individuals with multiple disabilities. Finally, though there was evidence of abnormal eye movements during reading, it is difficult to know whether the children had specific eye

movement deficits or whether the eye movement abnormalities during reading simply reflected their poor reading skills. The authors did report clinical identification of eye movement defects, but these were not documented or examined quantitatively using standard eye movement paradigms and there was no full term control group for comparison.

Downie et al. (2003) have drawn comparisons between the reading difficulties occurring in dyslexia and those occurring in preterm children. Given the magnocellular theory of dyslexia (Stein, 2001) and the fact that preterms with periventricular brain injury have visual dysfunction that may be due to damage of the magnocellular pathway (Jakobson et al., 2001, Jongmans et al., 1996), the authors investigated a group of children born at extremely low birth weight (<1000g) for the presence of magnocellular deficits and any association with reading or spelling problems. The magnocellular system has axons that have large receptive fields, detect motion and have fast conduction with poor sensitivity to fine detail or colour. They project to the primary visual cortex, from mainly peripheral retina and via the magnocellular layers of the lateral geniculate nucleus (Merigan & Maunsell, 1993). The dorsal visual stream is dominated by the magnocellular system, it projects to V5 and the parietal cortex and plays a major role in the visual guidance of eye movements (Milner & Goodale, 1995, Mishkin & Ungerleider, 1982). The magnocellular system therefore detects any visual motion and detects any retinal slip of an image, triggering the eyes to be repositioned on the object. The magnocellular theory of dyslexia suggests that

sensitivity to visual motion helps in the development of orthographic skills (ability to recognise the visual form of words) and if there is a defect in the magnocellular system, the poor motion sensitivity will additionally cause binocular instability resulting in jumbling of print and reading difficulties (Stein, 2001). The theory also suggests that motor impairments seen in dyslexia may be a result of the magnocellular deficits being passed to the cerebellum via projections to the posterior parietal cortex. In their study of preterms, Downie et al. (2003) investigated the magnocellular system using a motion defined form recognition test and also examined reading ability. The extremely low birth weight group (both with and without periventricular brain injury identified on ultrasound) scored very poorly on the motion processing task and the performance was significantly different to that of full term controls. Surprisingly though, there was no relationship found between motion processing ability and reading ability in the preterm children. The results are somewhat contradictory therefore, in that a magnocellular deficit was clearly identified in the preterm group but reading difficulty was not affected, contrary to the magnocellular theory of dyslexia. The authors suggest that a reading assessment including reading speed may more accurately predict magnocellular reading deficits. Though the magnocellular deficits were not correlated with reading ability, they were found to be characteristic of the preterms. This study did not assess the eye movements of the preterm children, but given the role of the magnocellular system in motion detection, this provides further evidence of the need to examine eye movements (particularly smooth pursuit) in preterms and also in relation to

reading ability. The lack of association between the magnocellular deficits and reading ability found by Downie et al. (2003) however, indicates discrepancies with the magnocellular theory that have been shared by others (Amitay et al., 2002, Chiappe et al., 2002, Ramus, 2003). The magnocellular theory predicts auditory, visual and motors deficits will coincide with the reading difficulties. However, the type of auditory, visual and motor deficits expected have often been absent in dyslexics (Amitay et al., 2002, Chiappe et al., 2002, France et al., 2002, Kronbichler et al., 2002, Olson & Datta, 2002, Ramus et al., 2003, Share et al., 2002).

4.7 Summary

Preterms are at increased risk of numerous cognitive and behavioural problems involving IQ and overall cognitive ability, spelling and speech, motor function, attention deficit and hyperactivity, executive function and personality traits. It is by no means just the preterms with major disabilities who suffer from problems in these areas. Nearly half of preterms have been found to have some academic and motor impairments and about a quarter of preterms have been found to have specific reading difficulties. This latter group have reading problems with normal IQ that cannot be attributed to an overall reduction in cognitive deficit. Other factors may be associated with the reading difficulties. The ocular requirements for reading include vision, saccades, vergence, accommodation and the binocular co-ordination of the eyes. Research investigating conditions other than preterms, has shown that eye movement deficits can contribute to reading difficulties.

Additionally, conditions such as strabismus, poor fusion, large near heterophoria, aniseikonia, anisometropia and poor accommodation can also cause reading problems. Research investigating reading and associated ocular and oculomotor deficits in preterms is extremely sparse. However, there is some evidence that preterms have poor control of eye movements during reading. There are also indications that preterms may suffer from magnocellular deficits, which though subject to controversy, has also been linked to dyslexia and could potentially affect smooth pursuit eye movement. Eye movement deficits could therefore be associated with or characteristic of the reading difficulties encountered by preterms with normal IQ.

CHAPTER 5: Methods

5.1 Introduction

To facilitate understanding of the rationale for the research and the aims and hypotheses that follow, a synopsis of the entire literature review is presented, highlighting the main issues raised.

5.1i Overall summary of the literature

Preterms have an increased risk of a variety of visual, binocular, ocular, oculomotor, cerebral, cognitive, behavioural, motor and specific reading deficits. Visual outcome may be impaired by disrupted visual development, cerebral visual impairment, retinopathy of prematurity, refractive errors and nystagmus. Preterms also have increased prevalence of strabismus which could lead to amblyopia and reduced levels of stereopsis. Cerebral damage may also occur, due to periventricular leukomalacia and intraventricular haemorrhage, and also from lesions affecting the cerebellum, thalamus, caudate nucleus and overall cortical volume. Many of the lesions affecting preterms may compromise structures involved in the oculomotor pathways. The control of the oculomotor system is complex and involves numerous cortical and subcortical areas. Examination of the various eye movement systems provides a unique method to explore the behaviour and function of different brain structures. The brain lesions in preterms may cause eye movement disorders as a result of damage to the pathways involving saccades, fixation, antisaccades, pursuit and vergence. Despite the likelihood of oculomotor deficits in preterms, this area has had

almost no quantitative investigation. Only one study was found that had used quantitative techniques and only pursuit maintenance was investigated in a small sample (Langaas et al., 1998). In addition to lesions directly affecting oculomotor control, certain aspects of oculomotor behaviour such as antisaccade performance and saccade/vergence latency have long developmental periods, and may be susceptible to developmental delay, in a similar way to the disruption that has been reported to affect the development of visual function. Preterms are also at increased risk of numerous cognitive and behavioural problems involving IQ and overall cognitive ability, spelling and speech, motor function, attention deficit and hyperactivity, executive function and personality traits. Nearly half of preterms have been found to have some academic and motor impairments and about a quarter of preterms have been found to have specific reading difficulties. This latter group have reading problems with normal IQ that cannot be attributed to an overall reduction in cognitive function. Other factors may be associated with the reading difficulties and research, although not using preterm subjects, has shown that eye movement deficits can contribute to reading problems. Additionally, conditions such as strabismus, poor fusion, large near heterophoria, aniseikonia, anisometropia and poor accommodation can also cause difficulty with reading. Research investigating reading and associated ocular and oculomotor deficits in preterms is extremely sparse. However, there is some evidence of preterms showing poor control of eye movements during reading. There are also indications that preterms may suffer from magnocellular deficits, which have also been linked to dyslexia, and could potentially affect smooth

pursuit eye movement. Eye movement deficits could therefore be associated with or characteristic of the reading difficulties encountered by preterms with normal IQ.

5.1ii Aims of the research

Preterm children have an increased ocular and cerebral morbidity and subsequently appear to be at increased risk of oculomotor deficits. Despite this, to my knowledge, there has been no quantitative investigation of the basic aspects of oculomotor control in children born preterm. The first aim of this study therefore was to quantitatively investigate the control of saccades, smooth pursuit and antisaccades in a group of preterm children in comparison to a group of full term controls of similar age. Preterms also have an increased incidence of problems affecting binocular control with an increased rate of strabismus and reduced levels of stereopsis. The second aim of this study was to investigate the control of binocular saccades, vergence and fixation. Children born preterm may have impaired visual function due to disruption in the visual development. Some aspects of oculomotor control have long developmental periods due to late maturation of areas of cerebral cortex and may also be susceptible to delayed development. The third aim therefore was to investigate the development of the control of antisaccades and vergence longitudinally, by examining preterms age 8-11 years and reassessing the same individuals at age 13-14 years. Aspects of oculomotor control are developing rapidly around this age. Another aim was to determine the extent of the development of vergence and antisaccades by assessing a cohort of preterms and full term controls of similar age at 15-16

years. Preterms have been found to have reading difficulties in the presence of a normal IQ, which therefore can not be attributed to an overall cognitive deficit and may be associated with other factors. The final aim was to investigate preterms for specific reading difficulties (SRD) and to determine whether there was any association between SRD and oculomotor control or orthoptic variables such as strabismus, stereopsis, near point of accommodation, accommodative amplitude and facility, convergence and fusional reserves.

5.1iii Hypotheses

This study will test the following groups of hypotheses:

i) Preterm children have impaired control of saccades, smooth pursuit and antisaccades compared to full term controls of similar age.

ii) Preterm children have impaired binocular control of saccades, vergence and fixation compared to full term controls of similar age.

iii) Preterm children show impaired development of eye movement control in the areas of vergence and antisaccades at the age of 13-14 years of age.

iv) Preterm children show continued impairment in the development of eye movement control in the areas of vergence and antisaccades at the age of 15-16 years of age.

v) Preterm children have specific reading difficulties in the presence of normal IQ that are associated with deficits in one or more of the following areas: oculomotor control, presence of manifest or latent strabismus, stereopsis, near point of accommodation, accommodative amplitude and facility, convergence and fusional reserves.

5.2 Experiments, recruitment and subject selection

5.2i Outline of experiments

The research described in this thesis is divided into four experimental sections. A summary of the different groups of subjects tested and the experiments in which they participated is given in Table 5.1.

Table 5.1 Groups of subjects tested, assessments performed and experiment type, (Sacc = saccades, SP = smooth pursuit, Asac = antisaccades, BSacc = binocular saccades, Fixn = fixation, Verg = vergence, Exp = experiment, shading denotes the groups involved in each experiment) *five extra full term subjects (not originally tested) were recruited due to a low number of original full term follow ups.

	GROUP 1 Age 8-11 yrs		GROUP 2 Age 10-11 yrs		GROUP 3 (retest group) Age 13-14 yrs		GROUP 4 Age 15-16 yrs	
	PT	FT	PT	FT	PT	FT*	PT	FT
Number of subjects	21	19	15	14	10	8	5	5
Oculomotor tests performed	Sacc SP Asac	Sacc SP Asac	BSacc Fixn Verg Asac	BSacc Fixn Verg Asac	Asac Verg	Asac Verg	Asac Verg	Asac Verg
Orthoptic assessment (yes/no)	Yes	Yes	Yes	Yes	No	No	Acuity only	Acuity Only
Reading assessed	Yes	Yes	Yes	Yes	No	No	No	No
Exp 1								
Exp 2								
Exp 3a								
Exp 3b								
Exp 4								

Experiment 1 investigated the monocular oculomotor control of saccades and smooth pursuit in preterm children aged 8-11 years (Group 1) and antisaccades in 8-11 year olds (Groups 1 and 2), in comparison with full term controls of similar age. Experiment 2 investigated the binocular oculomotor control of saccades, fixation and vergence in preterm children aged 10-11 years in comparison with full term controls of similar age (Group 2). Experiment 3 investigated the development of antisaccade and vergence control and consists of two subsections. Experiment 3a longitudinally investigated antisaccades (and vergence) in subjects originally tested in Experiment Groups 1 and 2, after a time period of three to five years, when the subjects were age 13-14 years (Group 3). However, the study design for vergence control had to be modified to a cross-sectional assessment due to recruitment problems, as explained in Chapter 8. Experiment 3b cross-sectionally investigated antisaccades and vergence in another group of preterms aged 15-16 years in comparison to full term controls of similar age (Group 4). Experiment 4 investigated the visual, binocular and oculomotor status of preterms in relation to reading performance (tested on subjects in Experimental Groups 1 and 2) and in comparison to full term controls.

5.2ii Recruitment and subject selection

Subjects were recruited after local ethics approval and informed consent was obtained. The investigation adhered to the tenets of the Declaration of Helsinki. Subjects comprising Groups 1 and 2 (and therefore subsequently Group 3) were recruited from a large cohort already identified and taking part in research

examining motor and cognitive outcome in preterm children (Foulder-Hughes & Cooke, 2003). The cohort was recruited by firstly identifying all preterm infants born before 32 completed weeks' gestation from 1991 to 1992 in eight hospitals within the Liverpool UK postal districts. Those who died before discharge from hospital or whose mothers were not resident within a Liverpool postal district at the time of birth were excluded. The subject's GP was contacted to ascertain current health status and school placement. Parents of those children who were alive and attending mainstream schools were recruited. The individual children's schools were then contacted and the teacher requested to choose a child of the same sex and same first language in the class, whose birthday was closest to that of the preterm child, to be the full term control. The preterm group comprised of 280 children with 210 full term controls. The full scale IQ of all children was tested using the short form of the Wechsler Intelligence Scale for Children UK, 3rd edition (WISC-III) (Wechsler, 1992). From this cohort preterm subjects and controls with normal IQ (≥85 i.e. a minimum of 1SD below the mean of 100) were identified and provide the source for Groups 1, 2 and 3. In addition to reduced IQ, subjects with a near uniocular LogMAR acuity of worse than 0.5 (6/19 Snellen) or who had a health status indicating a major neurological deficit such as cerebral palsy, blindness or deafness were excluded. Parents were approached via letter and provided with an information document and consent/assent form. Parents were requested to complete and return the consent/assent form in the supplied pre-paid envelope if they wished to take part. This process was repeated for the longitudinal aspect of Experiment 3a, by

sending out slightly modified letters and information documents to subjects in Groups 1 and 2, three to five years after they were initially tested to produce Group 3, with subjects aged 13-14 years. As recruitment of full term controls proved difficult for this group, extra full terms (not previously tested) age 13-14 years needed to be recruited. This was achieved by requesting help via the university intranet and via colleagues and again parents were provided with an information document and a consent/assent form. Preterm subjects in Group 4 were identified using the same inclusion criteria and from the same geographical area as the other groups, but they had not been previously tested in the study by Foulder-Hughes and Cooke (2003). The children were born in 1989 and aged 15-16 years when examined. Full term controls (aged 15-16 years) were recruited using the same methods as described previously (when obtaining extra subjects for Group 3) and informed consent was obtained.

5.3 Assessment of IQ

Subjects in Group 4 and the extra full terms in Group 3 had not been tested by Foulder-Hughes and Cooke (2003), and therefore had not had an IQ assessment. To ensure that the subjects were comparable to the other groups and met the inclusion criteria of an IQ score of 85 or above, a brief IQ assessment was performed using a subtest combination of the WISC-III. The WISC-III is a battery of tests for 6 to 17 year olds that evaluate intellectual abilities. It consists of two scales (each containing six subtests), vocabulary and performance, which combine to yield the full scale IQ (FSIQ). A short form of the WISC-III using the Vocabulary and Block-Design subtests can be used as a screening device to

identify abnormal IQ (Ryan, 1981). Research has identified Vocabulary as the best measure of g in the entire scale and Block-Design as the best measure of g among the performance subtests (Kaufman, 1975). The term g (originally devised by Spearman, 1904) refers to the general intelligence factor, which is considered to be the main component of an IQ measurement and common to the scores of all intelligence tests (Carroll, 1993). The Vocabulary and Block-Design subtests have high reliability and in combination yield a higher correlation with FSIQ than any other subtest pair (Goh, 1980). Ryan (1981) assessed 120 children with school or behavioural problems and found a high correlation of 0.78 for males and 0.88 for females, between the Vocabulary and Block-Design subtests and FSIQ. In addition no significant difference was found between the estimated IQ from the subtests and the IQ measured using the full scale. This is in agreement with other studies (Haynes, 1983, HerreraGraf et al., 1996) which also found satisfactory correlations (0.88 and 0.55-0.90); however they concurred with Ryan (1981) that whilst the subtest pair may be used as a screening device, it should not be performed in place of FSIQ when placement for special education is at stake or to make individual treatment programme decisions. The Vocabulary and Block-Design subtest pair was therefore a valid measure of IQ for screening purposes to identify subjects with abnormal IQ.

5.3i Vocabulary subtest

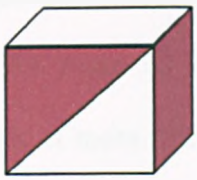
This test consists of 30 items of increasing difficulty. Each word is read to the child, who is required to respond with its meaning. The responses are judged for accuracy in relation to sample responses provided in the test book and awarded a

score of 2 points indicating good understanding, 1 point indicating an incorrect response, but some understanding and 0 points for lack of understanding. The test is discontinued if four consecutive failures are made. After the test the sum of the scores is calculated to provide a Vocabulary raw score.

5.3ii Block-Design subtest

This subtest comprises of nine blocks (cubes) with two red sides, two white sides and two red/white sides and a booklet containing ten designs of increasing complexity (figure 5.1).

a)



b)

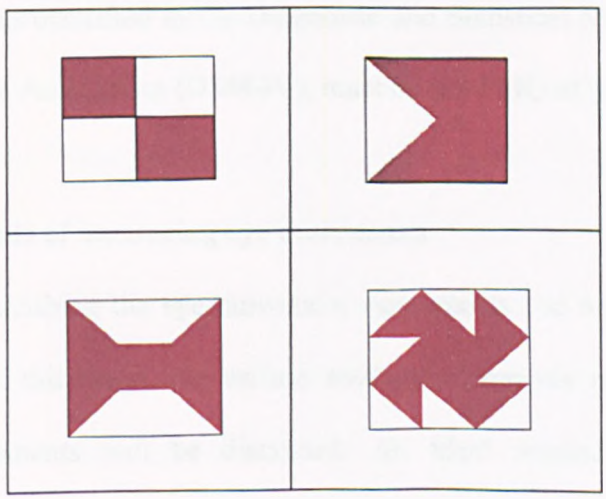


Figure 5.1 Block-design subtest, a) one of nine blocks used b) examples of the block designs showing increasing complexity

There are two, four and six block designs. The child is shown the first design and asked to replicate it manually using the blocks. The time taken to complete the task is recorded. The test is discontinued after two consecutive failures. Failure on an item can either be due to an inability to replicate the design precisely or failure to complete the task in the allotted time. Points are awarded for each correct design replicated with extra points given depending on the time taken to complete. The sum of the scores provides a Block-Design raw score. Raw scores from both subtests are converted to scaled scores, based on the child's age, using tables in the WISC-III manual. The sum of the scaled scores from both subtests can be converted, using a table (Appendix 3), to give an overall estimate of the FSIQ (Sattler, 1974). The mean IQ is 100 and one standard deviation is 15 (Wechsler, 1992). Scores of more than one standard deviation below the mean (<85) in line with other studies (Grunau et al., 2002, Saigal et al., 1992, Whitfield et al., 1997) are considered to lie outside the normal range, and specific learning disorders as classified in the Diagnostic and Statistical Manual of the American Psychiatric Association (DSM-IV), must have a FSIQ of ≥85 (APA., 1994).

5.4 Methods of measuring eye movements

Before describing the eye movement assessments and analysis for the research detailed in this thesis, the various methods commonly available for measuring eye movements will be discussed. An ideal method would measure eye movements throughout all three axes, have a high temporal and spatial resolution, without interfering with vision, touching the globe or being visible to

the subject. Also it would be unaffected by the level of illumination and movements of the head or be light enough that it could be fixed rigidly to the head of the subject (Carpenter, 1988, Collewijn et al., 1975). No system however satisfies all of these factors and a compromise must be made by choosing the system that most effectively meets the requirements for the experiment. Each system has relative advantages and disadvantages which will be discussed.

5.4i Electro-oculography (EOG)

An electrical field is present in the tissues surrounding the eye, thought to result from the permanent potential difference between the cornea and the fundus, in the region of about 1mV. As a result, small voltages can be recorded as the eye moves in the orbit by placing electrodes on either side of the eye. The precise origin of the corneoretinal potential is not known, as similar voltages have been recorded in a subject whose eye had been enucleated (Lippold & Shaw, 1971). It is not clear therefore how closely related the EOG potential is to the movement of the eye. The recorded potential may vary for reasons other than eye movement and has been shown to be influenced by the metabolic state of the eye (Marg, 1951), level of illumination (Gonshor & Malcolm, 1971), visual stimulation (Troelstra, 1972) and even velocity of the eye itself (Byford, 1963). EOG's therefore have been found to have a number of important drawbacks, are prone to drift and artefacts, are non-linear and require repeated calibration. Their advantages however are that they are relatively non-invasive, cause minimal discomfort, can accurately record a large range of horizontal movement (up to

40°) with spatial resolution of about 1° and are fairly inexpensive (Leigh & Zee, 1999).

5.4ii Infrared oculography

This measurement technique is based on the reflection of infrared light (which is unaffected by ambient lighting conditions) on both sides of the limbus from the white sclera and darker iris (Reulen et al., 1988). To record horizontal eye movement, infrared light emitting diodes and infrared light sensitive phototransistors are positioned above and below the eye respectively. Infrared light is projected onto the eye on both the nasal and temporal side and the phototransistor transforms the level of reflected infrared light into a voltage. The difference in voltage between the nasal and temporal phototransistors provides a signal that is proportional to the angular rotation of the eye. Horizontal movement can be recorded up to 30° with a spatial resolution of about 0.1° and temporal resolution of 1ms (Skalar Medical, Delft, Netherlands). This technique has the advantage that it is non-invasive, with little discomfort and good resolution and has been used successfully in children (Bucci et al., 2002). It has drawbacks however, as it can be unreliable for vertical eye movements, cannot record horizontal and vertical movements simultaneously in the same eye and requires stability of the head (Leigh & Zee, 1999).

5.4iii Scleral search coils

The scleral search coil method (Collewijn et al., 1975, Remmel, 1984, Robinson, 1963) has been widely used to measure eye position. Eye position is determined by placing a silicon annulus in the eye. The annulus contains a coil of thin copper wire. When the subject is placed in a magnetic field, the position of the eye can be determined from the amplitude of the induction current in the coil. The low noise of the coil allows for a very high spatial (up to 0.005°) and temporal (up to 4000Hz) resolution (Paperno & Semyonov, 2003) and it is regarded as the gold standard in oculomotor research (Collewijn, 1998). Although this system has the highest resolution of all techniques and is capable of measuring horizontal, vertical and torsional movements, it has some important drawbacks. It is invasive, can only be used for short periods at a time, is not really suitable for use with children and has been reported to cause increased intraocular pressure, buckling of the iris, corneal abrasion and reduced acuity (Irving et al., 2003). These effects were transient however, and others have reported contradictory findings with no changes in acuity, keratometry or intraocular pressure after search coil lens wear (Murphy et al., 2001).

5.4iv Video oculography

This method involves tracking of the pupil and its centre by the use of infrared cameras mounted either on a headband or remotely. Image analysis software determines the location of the pupil and maps the gaze position onto the visual field (which are usually stimulus images displayed on a computer monitor), via a

tracking algorithm. Small head movements can be compensated via a third camera monitoring the corners of the computer display. The advantages of this method are that it is easy to set up, is relatively insensitive to head movement and is non-invasive (Leigh & Zee, 1999). It has disadvantages however and is often criticised for having poor temporal resolution, with a standard frame rate of only 50-60Hz. Although this can be increased, it is usually at the expense of spatial resolution, which has made this technique inadequate for the examination of saccades with velocities up to 500°/s (Clarke, 1994). However, recent technological advances have led to improvements in temporal resolution with sample rates of up to 400Hz and a theoretical noise limited resolution of 0.01°. A recent study has compared properties of saccadic eye movements using this type of system with scleral search coils (van der Geest & Frens, 2002). Eye movements were recorded simultaneously by both methods during fixation and saccades. Fixation positions were well correlated between the video and coil output with an average discrepancy of less than 1° over a tested range of 40° x 40° of visual angle. Correlations were also high for saccade amplitude, duration and peak velocity (main sequence amplitude-peak velocity r^2=0.97, main sequence amplitude-duration r^2=0.99), though data on saccade latency was not presented. Video oculography therefore appears to be an alternative to scleral search coils but may not be suitable if accuracy of fixation of less than 1° is required and assessment involves small amplitude saccades (< 10°), where larger discrepancies were found. Recently 3D video oculography has been compared, simultaneously with scleral search coils (Houben et al., 2006). The video system

used had a sample rate of 200Hz and a spatial resolution of less than 0.1°. During a fixation task, positions were highly correlated for horizontal and vertical movement, but significantly different for torsional movements. In agreement with Van der Geest and Frens (2002) the saccade parameters were also well correlated between the two methods. Gains of torsion in relation to optokinetic stimuli were not significantly different. The results of this study indicated that video oculography may be a viable alternative for horizontal and vertical eye movements, though scleral search coils have far greater temporal resolution and greater accuracy for torsional movements.

5.4v Summary of eye movement techniques

As stated earlier, no method of measuring eye movements is free from drawbacks. Electro-oculography has the serious limitation that the results may have limited accuracy due to voltage changes for reasons other than changes in eye movement. At the opposite end of the spectrum scleral search coils have excellent spatial and temporal resolution, but are invasive making it unsuitable for use in children. Also the high resolution provided by the scleral search coils may only be needed if recording eye movements of very small amplitude, such as microsaccades. Video oculography technology has advanced in recent years, with improved sample rates and temporal resolution. These systems however are often expensive, and the accuracy may be reduced for small amplitude saccades (< 10°). For the purposes of the research described in this thesis, where the subjects were children, infrared oculography provided a good compromise, with

satisfactory levels of spatial and temporal resolution allowing accurate assessment of timing and accuracy of a wide range of horizontal eye movements, in a non-invasive manner. The experimental set up that was used is described in the next section.

5.5 Eye movement measurement

5.5i Experimental set up

Eye movements were recorded using the Skalar IRIS infrared limbus tracker (Cambridge Research Systems, Rochester, UK), with spatial and temporal resolution of < 1° and 1ms, respectively. The output from the eye-tracker was digitised with 16-bit precision at 1kHz using a CED Power 1401 interface (Cambridge Electronic Design, Cambridge, UK), and data written to hard disk for off-line analysis. Visual stimuli were generated on a computer monitor by a Visual Stimulus Generator 2/5 (Cambridge Research Systems, Rochester, UK). Subjects viewed the monitor at a distance of 57cms with their head stabilised by a chin/head rest and cheek pads. The target generated on the computer monitor for all tasks, was a small dark square on a light background (contrast 90%). Subjects wore a headset to which the infrared emitters and receivers were permanently fixed. The headset and position of the emitters/receivers were carefully adjusted whilst performing some trial saccades to ensure that a suitable gain and alignment was registered by the Skalar. For saccades (Experiment 1), pursuit and antisaccades, subjects viewed the targets monocularly with their left eye, the right eye was occluded. For the assessment of binocular saccades

(Experiment 2), fixation and vergence, subjects viewed the targets binocularly, and the right and left eye positions were recorded. After each task a calibration was performed and the subject was allowed to rest and the headset removed.

5.5ii Calibration

Calibration trials were collected immediately after the saccade, smooth pursuit, antisaccade and binocular saccade tasks. In Experiment 2 subjects completed both the fixation and vergence tasks (as they required less time to complete) followed by a single calibration task. The calibration task comprised of 24 trials and required the subject to execute either 5° or 10° visually directed reflexive saccades to the left or right, which were randomly interleaved. Each trial commenced with a fixation target appearing in the centre of the display for a random period of 0.5s-1.5s and the saccade target display time was 1s. The data was analysed off-line. For each of the 24 trials the amplitude of the total gaze shift was calculated (figure 5.2).

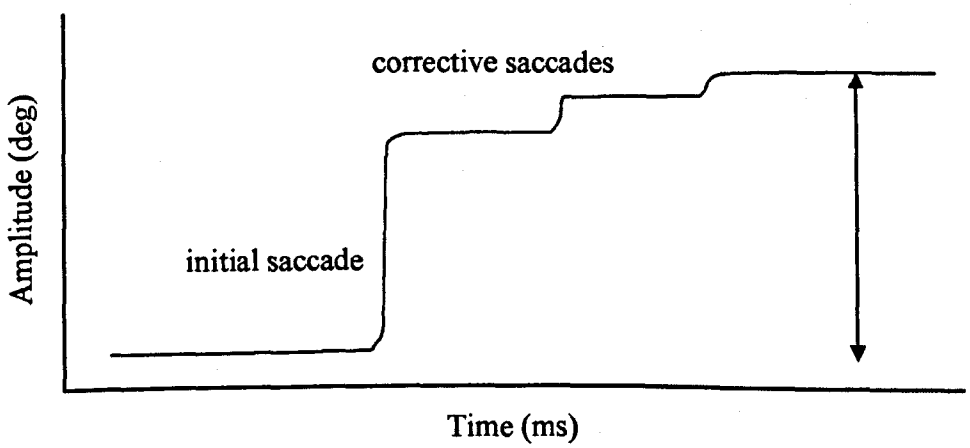


Figure 5.2 Measurement of a saccade in a calibration trial (amplitude of the total gaze shift indicated by the arrow)

Using Excel, the raw amplitude data were collated on the basis of the direction of the saccade (left or right) and the target amplitude (5° or 10°), and a linear regression performed of target amplitude versus the gaze amplitude. The slope of the regression line provided a calibration factor. For binocular data, calibrations were calculated for each eye separately.

5.5iii Measurement of saccades

The fixation target appeared in the centre of the display for a random period of 0.5-1.5s. The target stepped randomly 5° to the left or right of fixation. The subjects were instructed to view the fixation target and redirect their eyes as soon as they were aware of the target's new location, without attempting to move their head. Fifty-two trials were collected, immediately followed by 24 calibrations. The saccades were analysed off-line. Measurements were made on each of the 52 saccades unless contaminated by blinks or head movement. Saccade latency, duration, peak velocity and amplitude were calculated for each saccade (figure 5.3).

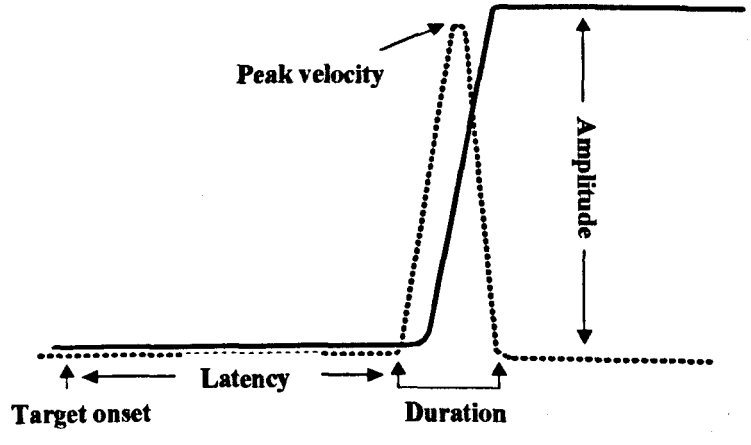


Figure 5.3 Diagrammatical representation of a saccade trace, indicating where the measurements of the different parameters were taken

Using the calibration factor, raw measurement data of the amplitude and velocity was converted into degrees and degrees/s, respectively. Saccade gain was calculated from the amplitudes by dividing the actual saccade amplitude by the desired target amplitude (5°) to provide an assessment of saccade accuracy. A value of less than one therefore indicated the saccade was hypometric and more than one indicated it was hypermetric. Mean values were calculated for leftward and rightward saccade gain, duration, latency and peak velocity for each subject. Saccade latencies of individual subjects were examined in more detail to determine the presence of express saccades. Express saccades are saccades with very short latencies (90-140ms) occurring as the first peak of a multimodal latency distribution, usually occurring during a gap task (Fischer & Ramsperger, 1984). However, express saccades can occur (although to a lower extent) in the overlap task and high percentages may reflect underlying pathology in brain areas controlling visual fixation and saccade initiation (Biscaldi et al., 1996). The number of express saccades (90-140ms) was recorded for each subject and the proportion of express saccades calculated (number of express saccades/number of valid trials). Statistical Package for the Social Sciences (SPSS) version 13.0 was used for statistical analysis.

5.5iv Measurement of antisaccades

As for reflexive prosaccades, the fixation target appeared in the centre of the display for a random period of 0.5-1.5s and then stepped randomly 5° to the left or right of fixation. The subjects were instructed to view the fixation target, but

this time when the target reappeared to the left or right of fixation, they were required to execute a saccade in the opposite direction but with the same amplitude (figure 5.4). Ninety-six trials were collected, immediately followed by 24 calibrations. At regular intervals (when completed ¼, ½ and ¾) throughout the trial the subjects were encouraged and reminded to look in the opposite direction.

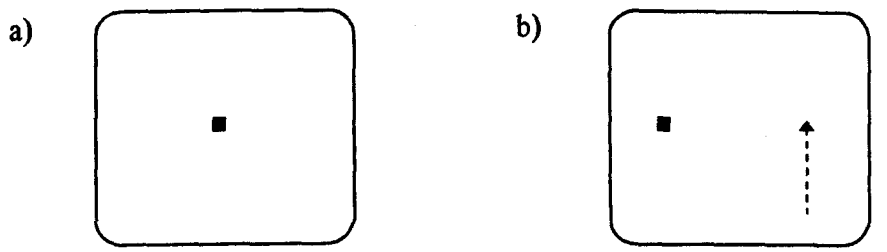


Figure 5.4 Antisaccade task a) subject views fixation target, b) target steps 5° to the left and the subject executes a voluntary saccade in the opposite direction from the target but with the same amplitude, the position of the antisaccade is indicated by arrow.

The antisaccades were analysed off-line, examining each of the 96 trials for each subject. The number of directional errors where a prosaccade was executed towards the target rather than an antisaccade was recorded. This was divided by the number of valid trials (trials where the trace was obscured by blinks or head movement were discarded) to produce an antisaccade directional error rate, expressed as a percentage. The number of discarded trials was also noted and a rejection rate calculated (number of discarded trials/total number of trials).

Where an error was made, the number of trials where the error was corrected with an antisaccade was recorded. This was expressed as the correction rate (number of trials where the antisaccade error was corrected/number of trials where an antisaccade error was made). Additionally, the latency of the both the incorrect prosaccade i.e. the antisaccade error (where an error was made) and antisaccade (where no error was made) were calculated, in the same manner as described previously for visually directed reflexive saccades. Mean values of the latencies were calculated for each subject. Also for the antisaccade errors, the number of express saccades (saccades occurring between 90-140ms) was calculated for each subject. The proportion of the antisaccade errors that were express saccades, expressed as a percentage, was calculated for each subject (number of express antisaccade errors/total number of antisaccade errors). Mean values of the various parameters were calculated in Excel and then entered into SPSS for statistical analysis.

5.5v Measurement of smooth pursuit

The fixation target appeared in the centre of the display for a random period of 0.5-1.5s, and then stepped randomly 5° to the left or right of fixation before moving at 14°/s back through the centre of display (a centripetal step-ramp, Rashbass, 1961). Subjects were instructed to view the fixation target and then follow the target in whichever direction it moved, to the end of the screen, then blink and prepare for the next trial. Fifty-two trials were collected, immediately followed by 24 calibrations.

Smooth pursuit latency, acceleration and velocity were measured for each trial. The initiation of pursuit was determined using a regression technique (figure 5.5) from trials in which the first eye movement after target appearance was a smooth movement i.e. pre-saccadic smooth pursuit.

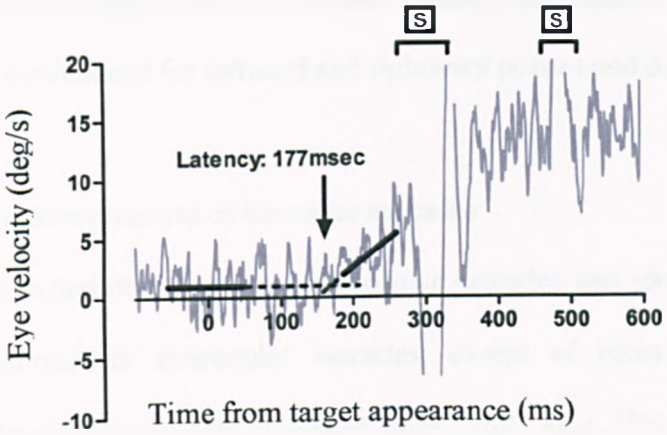


Figure 5.5 Example of a plot of eye velocity against time for a single rightward trial. Data from 100msec before to approximately 600msec after target appearance is shown. Two catch up saccades (S) occurred in this record, the first 121msec after the initiation of SP. The first regression (solid black line with zero slope) was fitted to the velocity data from approximately 50msec before to 50msec after target appearance. The second regression was fitted from 190msec to 275msec, during the acceleration phase of the response. The analysis program then calculated the intercept between the two functions, and calculated the pursuit latency (177msec in this example).

A regression of eye velocity on time was calculated from approximately 50ms before to 50ms after the appearance of the target, where the velocity would be expected to be zero. A second regression was calculated for the acceleration

phase of the pursuit response. The intercept between the two regression functions was taken as the time of pursuit initiation and the latency calculated. Eye velocity was measured, averaged over 20ms epochs, from 0 to 20ms and 80 to 100ms after the target appearance, 80 to 100ms after pursuit initiation at the end of the open loop period (figure 3.4) and finally 20ms centred on the peak slow eye velocity. Mean values of pursuit latency, acceleration and the four velocities were calculated for leftward and rightward pursuit and then entered into SPSS.

5.5vi Measurement of binocular saccades

The experimental set up of binocular saccades was identical to that previously described for monocular saccades, except of course, targets were viewed binocularly and data collected from both eyes. To determine the level of binocular co-ordination between the eyes and the extent of their disconjugacy, right eye position was subtracted from left eye position. This allowed the amount of saccadic disconjugacy and post-saccadic drift to be calculated (Collewijn et al., 1988, Fioravanti et al., 1995, Kapoula et al., 1986). Positive values indicated convergent disconjugacy (as saccades to the left were negative) and divergent values indicated divergent disconjugacy (figure 5.6). Firstly the amplitude of the saccadic disconjugacy was measured, indicated by the peak on the subtracted trace. The amplitude of disconjugacy was then measured at the onset of the target (i.e. before the saccade) and 75ms and 150ms after the saccade offset (figure 5.7).

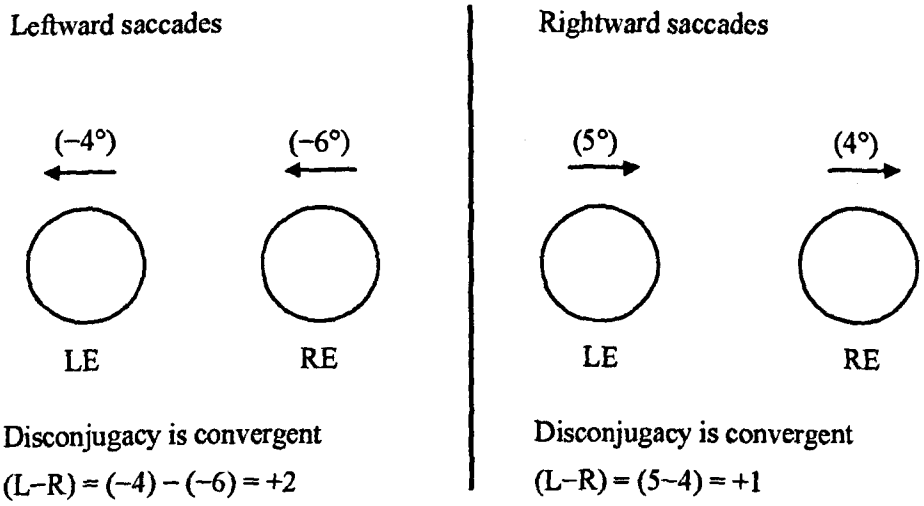


Figure 5.6 Example of saccadic disconjugacy for leftward and rightward saccades, demonstrating how the sign (+ or −) identifies the type of disconjugacy. The arrow indicates the direction of the eye movement and the saccade amplitude is in parentheses.

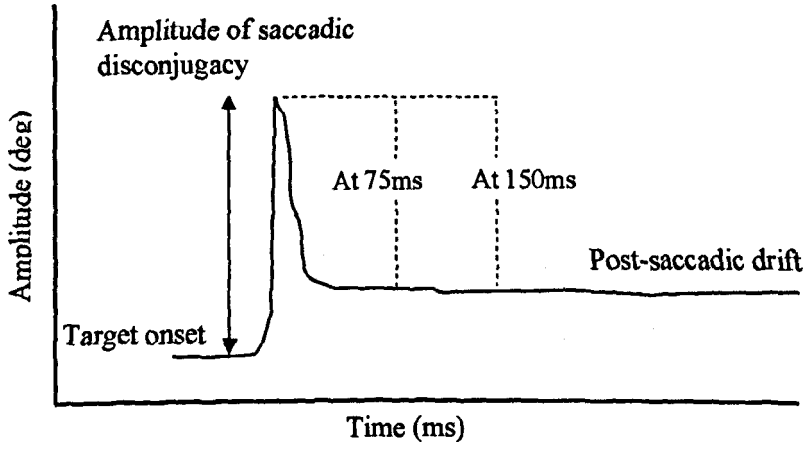


Figure 5.7 Diagrammatical representation of a subtracted binocular trace, showing the points where the disconjugacy was measured (the saccade, at target onset and at 75ms/150ms from the peak i.e. saccade offset)

This time period was chosen because after 160ms the saccade includes visually driven components and the measurements were aimed at assessing the earlier drift components, related to the pulse-step signals (Kapoula et al., 1997). Post-

saccadic drift was calculated by subtracting the amplitude of disconjugacy at the target onset from the amplitudes at both 75ms and 150ms after the saccade offset. Mean values of the convergent/divergent saccadic disconjugacy and post-saccadic drift at 75ms and 150ms for leftward and rightward saccades were calculated (the + and − signs were ignored once the type of disconjugacy had been identified). Disconjugacy is predominantly divergent in adults but less so for children (Fioravanti et al., 1995, Yang & Kapoula, 2003). To assess this, the proportion of divergent disconjugacy was calculated for both the saccadic disconjugacy and post-saccadic drift (at 75ms and 150ms). All data was entered into SPSS.

5.5vii Measurement of vergence

Subjects viewed a fixation target in the centre of the display for a random period of 0.5-1.5s. Disappearance of the target was the cue to execute a vergence movement, to a target positioned centrally at a distance of 10cm from the subject, requiring a vergence shift of 25° (figure 5.8). The target was a letter of vertical height 0.2cm (visual angle 1.1°), positioned in horizontal and vertical alignment with the eyes. Vertical head adjustment was made by means of the chin rest and by instructing the subject to view one of three vertically displaced letters (figure 5.9).

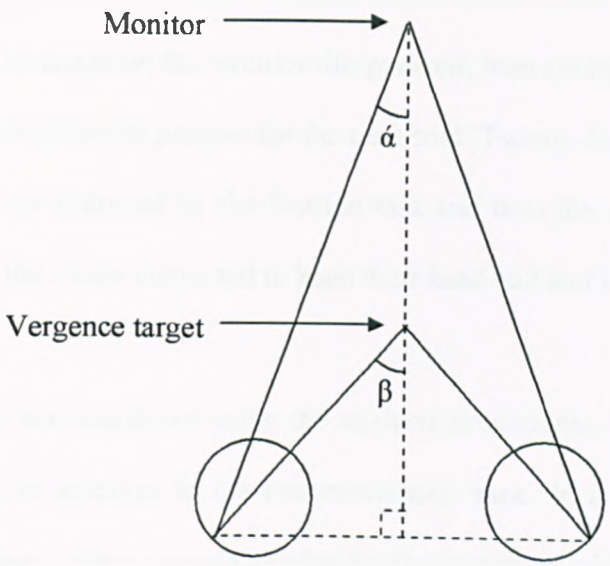


Figure 5.8 Vergence shift required to moves the eyes from the monitor to the target, vergence shift = (β – α) x 2; (15.4°-2.8°) x 2 = 25° (based on inter-pupillary distance of 5.5cm).

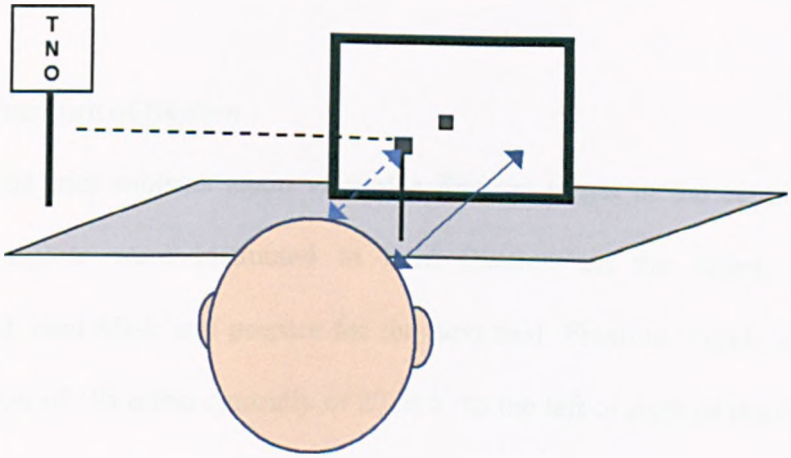


Figure 5.9 Vergence set up. The subject viewed a monitor at a distance of 57cms (⟷). The fixation target was place at 10cms (⟷) from the subject, requiring a vergence shift of 25°.

The subject was instructed to move their eyes towards the vergence target as soon as the target on the monitor disappeared, then count to two and return their eyes to the screen to prepare for the next trial. Twenty-four trials were collected, immediately followed by the fixation task and then the calibration task. During this time they were instructed to keep their head still and not to touch the headset.

Each trial was examined using the analysis programme. The velocity trace was displayed in addition to the eye movement trace. In a similar manner to the measurement of the saccade amplitude, the amplitude of the vergence angle was measured from the trace. The start of vergence was taken to be when the eye velocity exceeded 5°/s (Yang et al., 2002), and the difference between this and target onset provided the vergence latency. Additionally the time to peak vergence velocity and peak velocity were measured. All measurements were performed for each eye. Mean values of these values were entered into SPSS.

5.5viii Assessment of fixation

To begin the trial subjects again viewed a fixation target in the centre of the display. Subjects were instructed to hold fixation on the target, until it disappeared, then blink and prepare for the next trial. Fixation targets appeared for a duration of 10s either centrally or 2° or 5° to the left or right of the centre of the display. Twenty trials were collected, comprising of four trials at each position. This task was immediately followed by 24 calibrations.

The control of fixation was assessed by examining the trials for square wave jerks and any 'other saccadic' intrusions (figure 5.10). Square wave jerks (SWJ) were defined as an initial saccade away from the target (of less than 3°) followed by a corrective saccade at least 100ms but no more than 400ms after the initial saccade (Shaffer et al., 2003). The presence of saccadic intrusions not falling into this definition (referred to as 'other saccadic' intrusions) were examined and defined as shifts in fast eye movement during the fixation of velocity greater than 70 deg/s (Munoz et al., 2003). The rate of SWJs (and 'other saccadic' intrusions) per second was calculated by dividing the number of occurrences by the total number of seconds spent fixating. The peak velocity, amplitude and duration of SWJs and all 'other saccadic' intrusions were measured. The SWJ and 'other saccadic' intrusion rate and means of peak velocity, amplitude and duration were entered into SPSS.

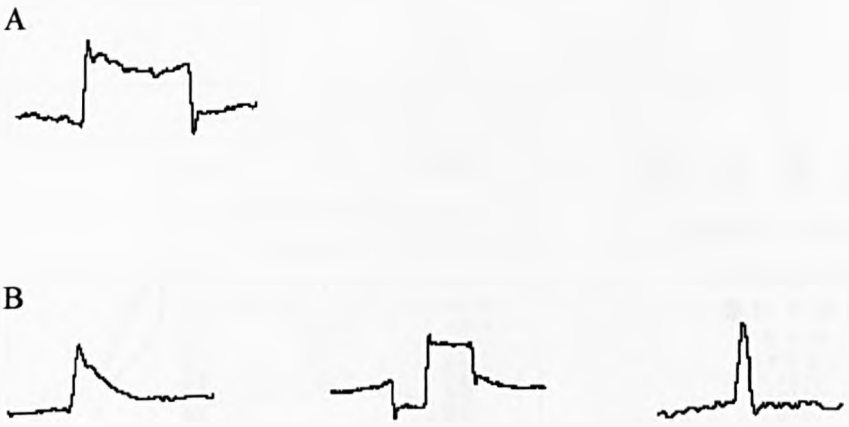


Figure 5.10 Examples of a square wave jerk (A) and 'other saccadic' intrusions: single saccadic pulse, biphasic square wave intrusion and double saccadic pulse (B); adapted from Abadi and Gowen (2004)

5.6 Visual and binocular assessment

In addition to eye movement control, a visual and binocular assessment was also performed, including measurement of visual acuity, strabismus assessment and measurement, fusion range, stereopsis, convergence and accommodation. Values from each assessment were entered into SPSS.

5.6i Visual acuity

Visual acuity was tested uniocularly at near (40cm, figure 5.11a) and distance (4m figure 5.11b) using a LogMAR chart (Precision Vision, La Salle, IL, UK). Each row on the chart has five letters and each letter has a value of 0.02. The line of letters indicating normal acuity has a score of 0.0. For each letter that is not correctly identified 0.02 is added, and for every additional letter correctly identified 0.02 is subtracted. Acuity that is better than average therefore has a negative score.

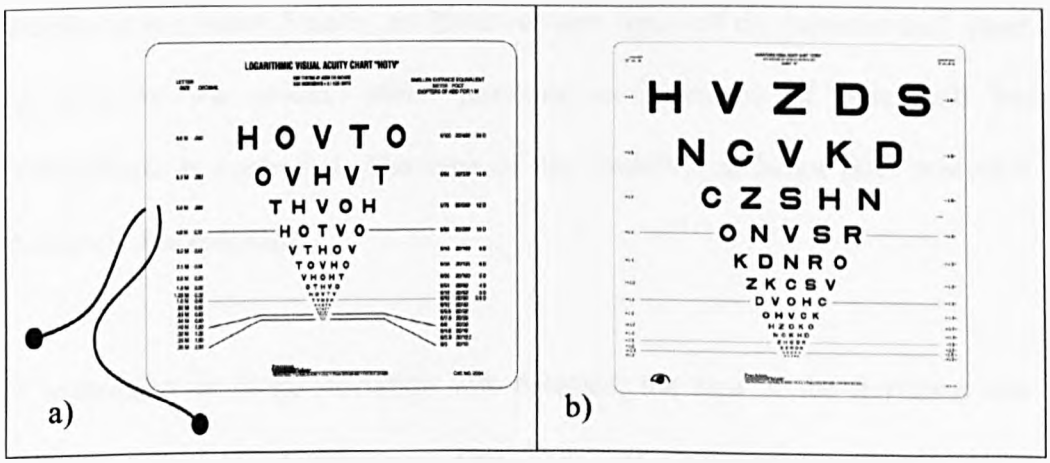


Figure 5.11 a) Near LogMAR, b) Distance LogMAR

The LogMAR is considered to be the gold standard of acuity measurement as unlike Snellen, it has an equal number of letters per line, equal distance between the letters and lines and equal progression between the sizes of letters from one line to the next (Bailey & Lovie, 1976).

5.6ii Strabismus assessment and measurement

The cover/uncover and alternate cover tests were performed to determine the presence of manifest or latent strabismus. Corneal reflections were assessed initially, checking for asymmetry and displacement of a reflection which would indicate a manifest strabismus. Either eye was then covered and uncovered whilst the subject fixated a near and distance target. An outward or inward movement of the uncovered eye when the eye was occluded indicates the presence of an esotropia or exotropia respectively. The eyes were then covered alternately (alternate cover test) and the eye observed as the cover was removed. An outward movement indicates an esophoria and an inward movement indicates an exophoria is present. Finally, as the cover was removed the presence and speed of recovery was noted, which provides an indication of how well the heterophoria is controlled. The type of any manifest or latent (and recovery) deviation was recorded.

If a manifest or latent deviation was detected, the size of the deviation was measured using the prism cover test. This was performed at either near or distance (or both), with either a horizontal or vertical prism bar, as appropriate.

The deviation was measured by increasing the prism strength whilst performing an alternate cover test. As the prism strength increases the movement of the eye seen on the cover test reduces, is neutralised and then reverses. The point prior to reversal indicates the angle of deviation. The size of the manifest or latent deviation (in prism dioptres) was recorded.

5.6iii Fusion range

The prism fusion range assesses motor fusion which is the ability to maintain sensory fusion through a range of vergence. The prism fusion range, noting both the blur and break point (Melville & Firth, 2002) was examined at both near and distance. A prism bar (base out) was introduced whilst the subject viewed a letter (commensurate with the maximum acuity) at a third of metre (near test) or six metres (distance test). The prism was increased and the subject asked to report when the target initially became blurred (blur point) and then became double (break point). This was repeated with the prism base in. The base out prism assesses the convergent range and base in assesses the divergent range. The blur point is reached when the subject has used all available fusional reserves and has to use accommodative convergence to keep the target fused. As accommodative convergence is exerted the extra accommodation causes the target to become blurred. The break point occurs when the subject no longer has any fusional or accommodative vergence remaining and results in the break of fusion and diplopia (Esperjesi, 2000). The near and distance blur and break points were recorded.

5.6iv Stereopsis

Stereopsis is the ability to perceive depth and the highest grade of binocular vision. Stereopsis was assessed using the TNO test (Lameris Ootech BV., Nieuwegein, Netherlands), which uses random dot stimuli with red and green glasses to separate the images presented to either eye. There are no monocular clues and the stereotarget is not outlined by monocularly visible contours. The disparities range from 1980 to 15 seconds of arc. The subjects were required to identify a stereoscopic shape of reducing disparity until a threshold was reached. The maximum level of stereopsis corresponding to the minimum amount of disparity detected was recorded.

5.6v Convergence

The near point of convergence is the point at which binocular convergence fails as an object is brought towards the eyes, resulting in diplopia which normally occurs at 6cm (Hayes et al., 1998). This was assessed using the RAF rule (Haag–Streit UK, Harlow, UK). The subject was instructed to view the side of the drum displaying the dot target, positioned at 33cms. The drum was advanced towards the subject slowly and smoothly until the subject reported diplopia. The distance of the target when this occurred was recorded as the near point of convergence. The test was performed three times to detect the presence of fatigue.

5.6vi Accommodation (near point, amplitude and facility)

The near point of accommodation is the nearest point at which an object can be seen clearly. The near point of accommodation was assessed in a similar manner to the near point of convergence. The RAF rule was used and the subject asked to view the side of the drum displaying the reduced Snellen chart. A letter was chosen that was commensurate with the subject's level of acuity. The Snellen letter was viewed at a third of a metre and the drum advanced slowly towards the subject until they reported that the letter had become blurred. This distance of the letter was recorded as the near point of accommodation. The test was performed binocularly and then uniocularly with the left and right eye and repeated three times to check for fatigue. Values can be compared to those expected, based on the Hofstetter formula (Hofstetter, 1950) which states that the average amplitude is 18.5-subject's age/3 and the minimum expected amplitude is 15-subject's age/4 (table 5.2).

Table 5.2 Expected amplitude of accommodation based on Hofsetter's formula

Age (years)	10	15	20	25	30	35	40	45	50	60
Minimum accom (D)	12.50	11.25	10.00	8.75	7.50	7.00	5.00	3.75	2.50	0.00
Mean accom (D)	15.17	13.50	11.84	10.17	8.50	7.84	5.18	3.50	1.85	0.00

Another method of assessing accommodation is to determine the amplitude using lenses. At a distance of 6m, the subject was asked to view a letter at the level of

their maximum acuity. Convex lenses were introduced (to relax their accommodation) starting with 0.25DS and increasing in 0.25DS intervals, until the letter became blurred. The maximum amount of accommodation that could be relaxed was noted. The test was then repeated with concave lenses in 0.50DS intervals and the maximum amount of accommodation exerted was noted. The two values (relaxed and exerted accommodation), irrespective of their sign, were added together to give the amplitude of accommodation. The test was performed both binocularly and uniocularly.

The final assessment of accommodation was via a measure of accommodative facility (Goss, 1992). Accommodative facility is the speed at which clarity is restored following a rapid change of focus. This was tested using flipper lenses (Kay Pictures, Tring, UK) with +2.00DS/-2.00DS lenses (figure 5.12).

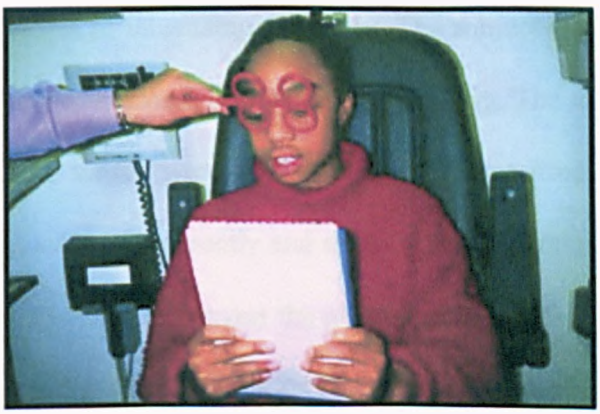


Figure 5.12 Use of flipper lenses to assess accommodative facility

The subject viewed a word from a Maclure reading book at 40cms at a level commensurate with their maximum acuity. The -2.00DS lenses were introduced and the subject was instructed to report when the text became clear. When the text was clear the lenses were flipped and the +2.00DS lenses introduced. Again the subject reported when the text was clear. The ability to focus the text through both the positive and negative lenses constituted one cycle. The test was timed and the number of complete cycles per minute recorded. The test was performed binocularly and then monocularly.

5.7 Assessment of reading ability

Reading ability was assessed by two methods, The Graded Word Reading Test (NFER-NELSON Publishing Company Ltd., Windsor, UK) and the Neale Analysis of Reading Ability – Revised (NARA II, NFER-NELSON Publishing Company Ltd., Windsor, UK). The Graded Word Reading Tests consists of a card listing 50 words of increasing difficulty. The subject was given the card and asked to read the words aloud, without any prompting. The test was discontinued if five consecutive words were read incorrectly or omitted. A score of one is given for every word read correctly and the total represents the raw score. A table in the test manual is used to convert the raw score, dependent of the subject's age at testing, into a standardised score. As the score is standardised (as for the IQ) it therefore has a mean of 100 and a standard deviation of 15 (figure 5.13).

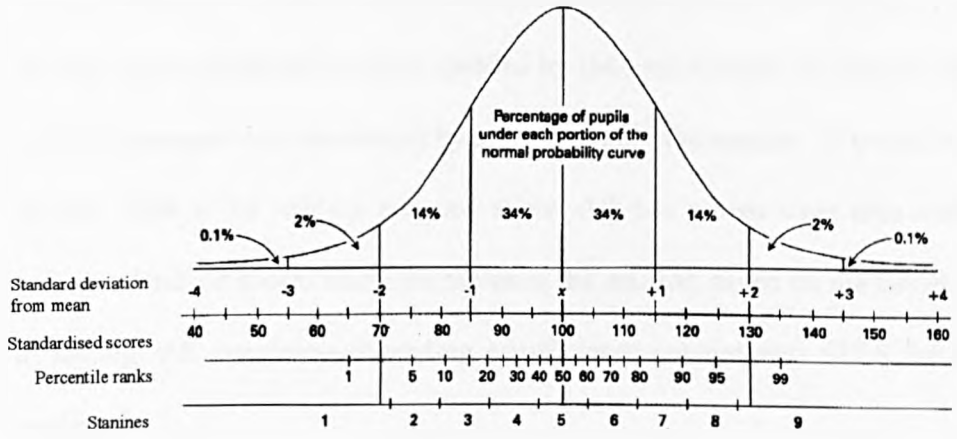


Figure 5.13 Normal distribution showing the relationship of the standardised scores, standard deviations and percentile ranks

The Neale Analysis of Reading Ability assesses reading accuracy, rate and comprehension. The test comprises of six passages. Subjects were asked to read the first passage aloud whilst any errors such as mispronunciation, omissions, additions, substitutions, reversals or refusals were noted. Repetitions, hesitations and self-corrections were not counted as errors. The time taken to read the passage was recorded in seconds. Immediately after the passage had been read subjects were asked a total of eight questions about the story to test their comprehension. The test then continued with the next passage. The test was discontinued when more than sixteen errors were made on any passage. The number of correct answers for each comprehension test is totalled to provide a comprehension raw score. The accuracy raw score is determined by subtracting the number of errors made on each passage from the designated maximum attainable (16 for passages 1-5 and 20 for passage 6). The sum of the scores for

each passage gives an overall raw accuracy score. The number of words read in each passage are added together, divided by the total number of seconds taken to read the passages and multiplied by sixty to obtain the number of words read per minute. This is the reading rate raw score. All raw scores were then converted into standardised scores using the tables in the manual, based on the subject's age at testing. All standardised reading scores were entered into SPSS for further analysis.

In line with previous research (Fletcher et al., 1994, Taylor et al., 1995) and as discussed in Chapter 4, reading difficulties were identified using the low achievement definition. Children who achieved below average standard scores (<85) on one or more assessments of reading ability were identified as having a reading difficulty.

CHAPTER 6: Control of saccades, smooth pursuit and anti-saccades in children born preterm vs. full term (Experiment 1)

Measurements of saccades and smooth pursuit were collected on 21 preterm and 19 full term children (Group 1). Technical problems with recording data of one full term meant that pursuit measurements were only available for 18 full terms. Antisaccade measurements were attempted on 36 preterms and 33 full terms (Groups 1 and 2), but one subject in each group became distressed prior/during testing and the recording had to be abandoned. Antisaccade measurements were therefore collected on 35 preterms and 32 full terms. Generally both preterm and full term subjects coped well with the tests they were asked to perform, with no notable differences between the groups. Time for testing typically ranged between 50 and 60 minutes, including time for breaks.

The demographics of both groups are presented in Table 6.1. The demographic data for both preterms and full terms (Groups 1 and 2) was normally distributed, as determined by the Kolmogorov-Smirnov test (Appendix 2.1). To determine any difference between preterms and full terms for age and IQ, an unpaired t-test was used. There was no statistically significant difference in the mean age between PTs and FTs for either Group 1 ($t=0.176$, $p=0.9$) or Group 2 ($t=-0.204$, $p=0.8$) indicating that both PTs and FTs were well matched for this variable. The mean IQ was slightly higher in FTs than PTs for both Group 1 ($t=3.076$, $p=0.004$) and Group 2 ($t=3.948$, $p<0.001$), but all PTs had IQ greater than 85 and therefore well within the normal range.

Table 6.1 Demographics of preterm and full term children recruited for Experiment 1, K-S stat = Kolmogorov-Smirnov test statistic Z

	Saccades and Smooth Pursuit		Antisaccades	
	Preterm	Full term	Preterm	Full term
Number of subjects	21	19	35	32
Mean age when tested (months) and range	114.8 101-131	115.3 100-140	121.3 101-143	121.9 100-142
Mean full scale IQ and range	97 85-113	105 91-119	98 85-113	105 91-121
Mean GA (weeks) and range	30.0 24-32	37+	29.9 23-32	37+
Mean birth weight (g) and range	1388 512-2220	N/A	1421 512-2300	N/A

6.1 Statistical analysis

The normality of the distribution of the saccade, pursuit and antisaccade data was determined using the Kolmogorov-Smirnov test. All of the eye movement data, except for the proportion of express saccades in the standard prosaccade task were normally distributed for both preterm and full term children. The proportion of express saccades for the standard prosaccade task was therefore analysed using a non-parametric test (Mann-Whitney U Test). As the remaining data was both continuous and normally distributed, the unpaired t-test was used to compare the means. Levene's test was used to check for equality of variance between the means and the appropriate p value was recorded.

6.2 Control of saccades

The distribution of measurements of saccade gain, latency, peak velocity, duration and proportion of express saccades were assessed using the Kolmogorov-Smirnov test. The data were found to be normally distributed except for the proportion of express saccades in preterms (Appendix 2.2). Due to reports of potential directional differences (Honda, 2002) analysis was performed separately for leftward and rightward saccades.

An example of the saccade traces for a preterm and full term subject are provided in Figure 6.1. Saccade accuracy as determined by the mean saccade gain was not significantly different between preterms and full terms (table 6.2). As reflected in the standard deviations, there was slightly more variability between the individuals in the preterm group compared to the full terms (figure 6.2). Levene's test revealed that the difference in variance in saccade gain between the groups was not significant for leftward saccades ($F=0.01$, $p=0.9$) but approached significance for rightward saccades ($F=3.45$, $p=0.07$).

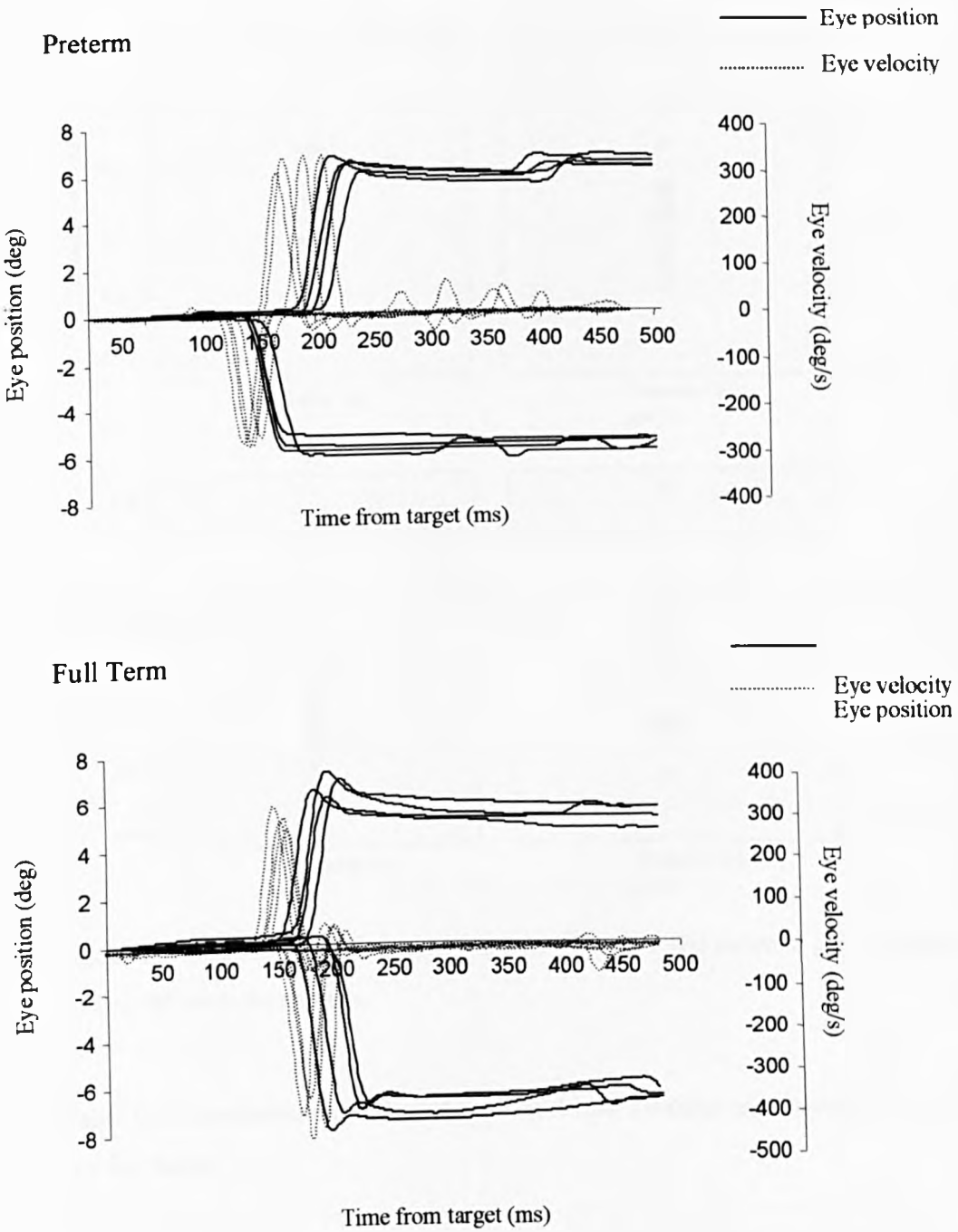


Figure 6.1 Examples of 4 saccade traces (leftward and rightward) showing the eye position and velocity in a single preterm (top) and full term (bottom) subject. Though the selected traces for the preterm subject show directional differences this was not characteristic of all of the traces, nor the preterm group.

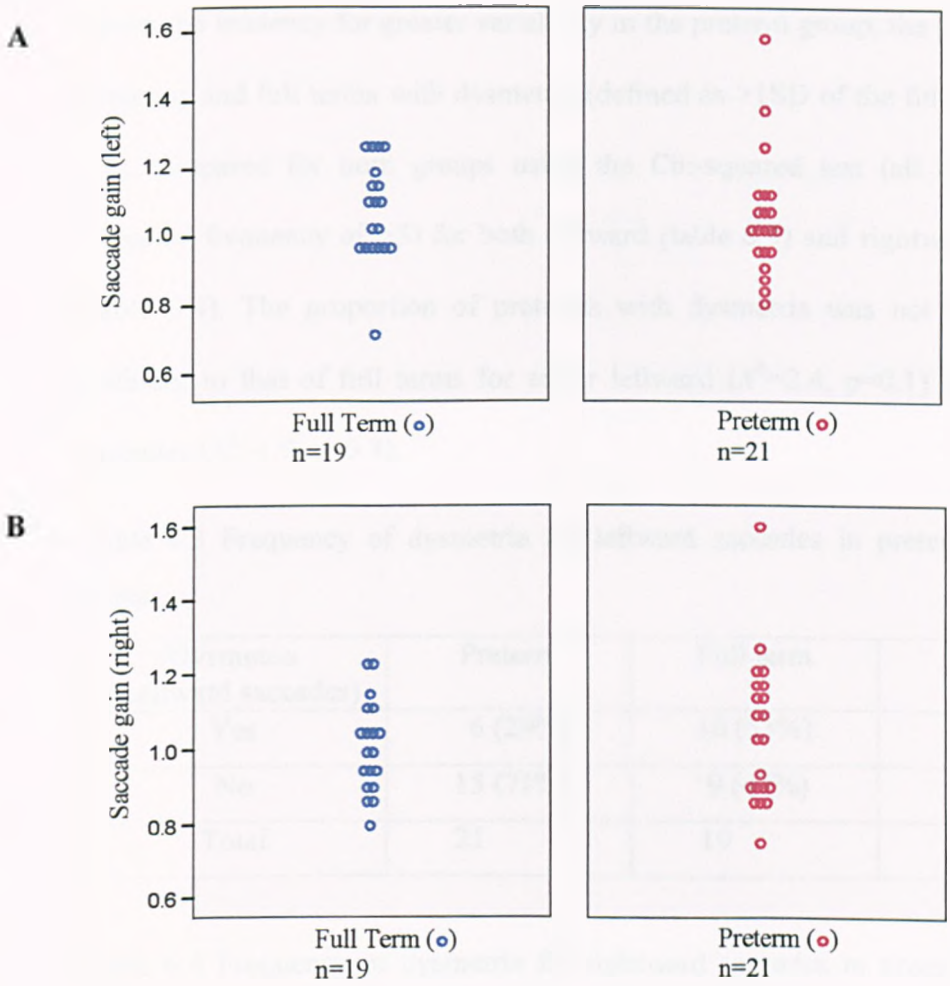


Figure 6.2 Distribution of leftward (A) and rightward (B) saccade gain in preterm (o) and full term (o) subjects

Table 6.2 Comparison of leftward and rightward saccade gain between preterms and full terms

Saccade Gain	Preterms mean±sd	Full terms mean±sd	Significance
Leftward	1.06±0.17	1.07±0.14	p=0.8
Rightward	1.07±0.19	1.01±0.12	p=0.3

Given the tendency for greater variability in the preterm group, the proportion of preterms and full terms with dysmetria (defined as >1SD of the full term mean) was compared for both groups using the Chi-squared test (all cells had an expected frequency of >5) for both leftward (table 6.3) and rightward saccades (table 6.4). The proportion of preterms with dysmetria was not significantly different to that of full terms for either leftward (X^2=2.4, p=0.1) or rightward saccades (X^2=1.0, p=0.3).

Table 6.3 Frequency of dysmetria for leftward saccades in preterms and full terms

Dysmetria (Leftward saccades)	Preterm	Full term	Total
Yes	6 (29%)	10 (53%)	16
No	15 (71%)	9 (47%)	24
Total	21	19	40

Table 6.4 Frequency of dysmetria for rightward saccades in preterms and full terms

Dysmetria (Rightward saccades)	Preterm	Full term	Total
Yes	11 (52%)	7 (37%)	18
No	10 (48%)	12 (63%)	22
Total	21	19	40

Saccade latencies were slightly longer for preterms compared to full terms (table 6.5) but the differences were not statistically significant. Again there was slightly more variation in the latencies in the preterm group compared to the full terms (figure 6.3), though the difference in variance was not statistically significant (L: F=1.17, p=0.3; R: F=0.15, p=0.7).

Table 6.5 Comparison of leftward and rightward saccade latencies between preterms and full terms

Saccade latency (ms)	Preterms mean±sd	Full terms mean±sd	Significance
Leftward	206.2±43.3	200.1±30.0	p=0.6
Rightward	210.4±37.8	204.8±33.5	p=0.6

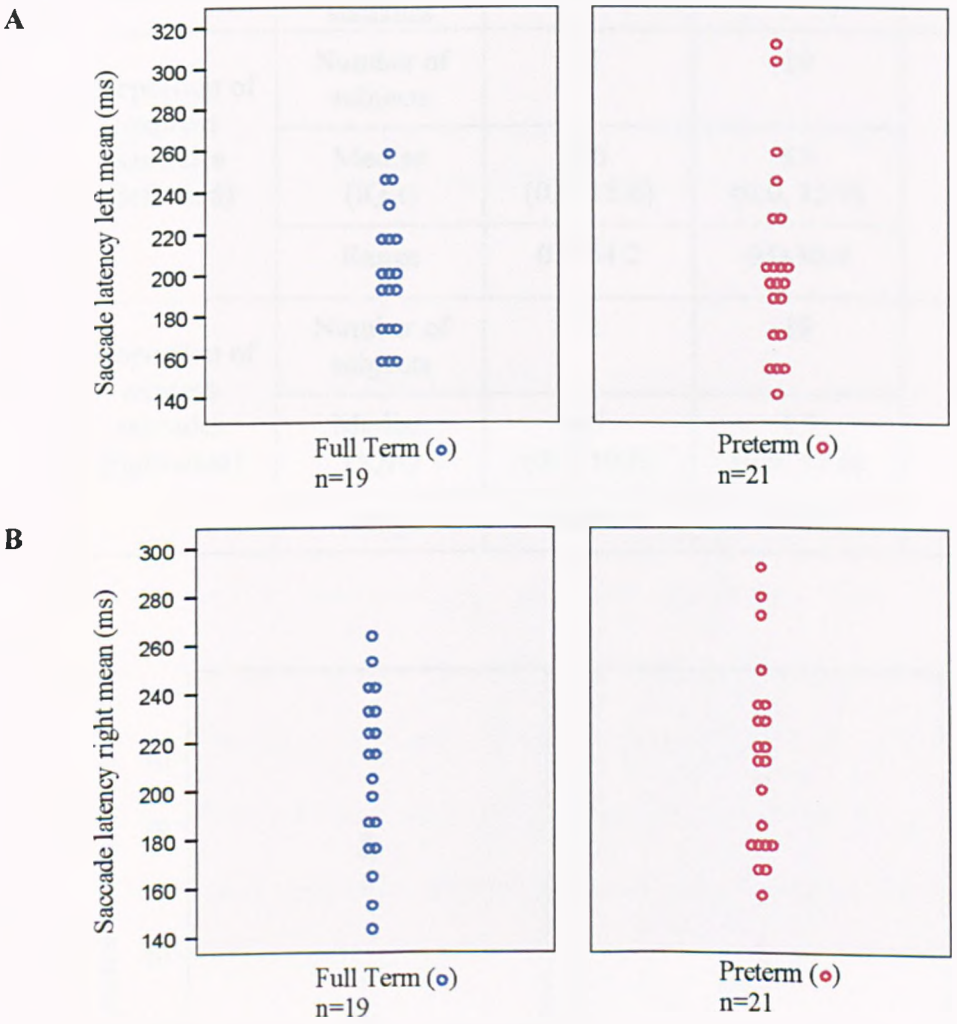


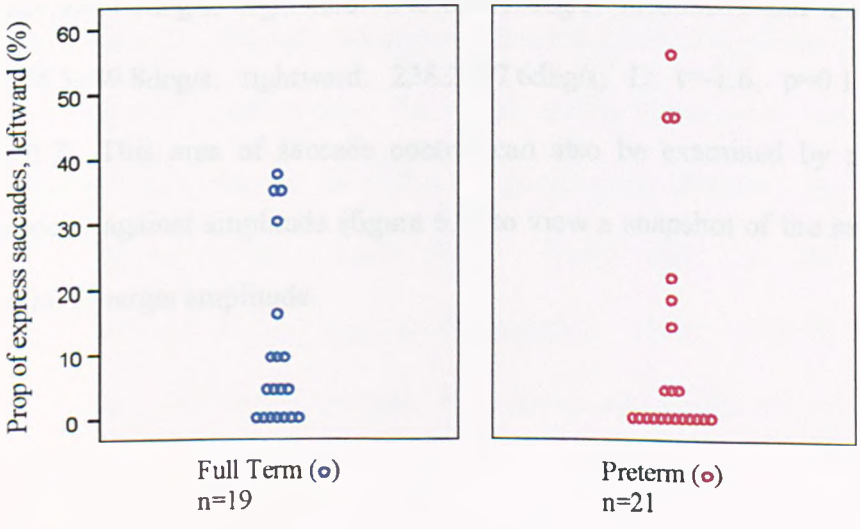
Figure 6.3 Distribution of leftward (A) and rightward (B) saccade latencies in preterm (o) and full term (o) subjects

The saccade latencies of individual PT and FT subjects were examined to determine the proportion of saccades where latencies were between 90-140ms i.e. express saccades (table 6.5). The proportion of express saccades was similar for both preterms and full terms with a wide range in both groups (figure 6.6).

Table 6.6 Comparison of the proportion of express saccades (leftward and rightward) between preterms and full terms

Parameter	Descriptive statistics	Preterms	Full terms	Significance
Proportion of express saccades (leftward)	Number of subjects	21	19	p=0.4
	Median (IQR)	0.0 (0.0, 15.6)	4.3 (0.0, 15.7)	
	Range	0.0-54.2	0.0-36.4	
Proportion of express saccades (rightward)	Number of subjects	21	19	p=1.0
	Median (IQR)	4.3 (0.0, 10.6)	4.3 (0.0, 17.6)	
	Range	0.0-29.2	0.0-47.8	

A



B

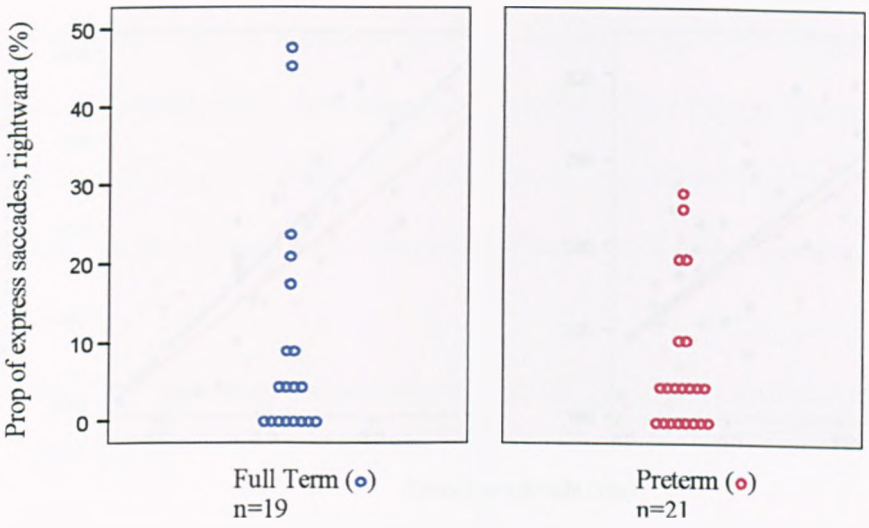


Figure 6.4 Distribution of the proportion of express saccades (leftward, A and rightward, B) in preterm (o) and full term (o) subjects

The mean saccade duration was slightly longer for PTs (leftward: 45.8±6.9ms, rightward: 44.3±5.7ms; mean±sd) compared to FTs (leftward: 42.9±4.5ms, rightward: 42.8±3.9ms) but was not statistically significant (L: t=-1.5, p=0.1; R: t=-1.0, p=0.3). Peak velocity was also similar for both PTs (leftward: -229.9±44.1deg/s, rightward: 243.0±47.1deg/s; mean±sd) and FTs (leftward: -254.5±49.8deg/s, rightward: 238.2±37.6deg/s; L: t=-1.6, p=0.1, R: t=-0.4, p=0.7). This area of saccade control can also be examined by plotting peak velocity against amplitude (figure 6.5) to view a snapshot of the main sequence at the 5° target amplitude.

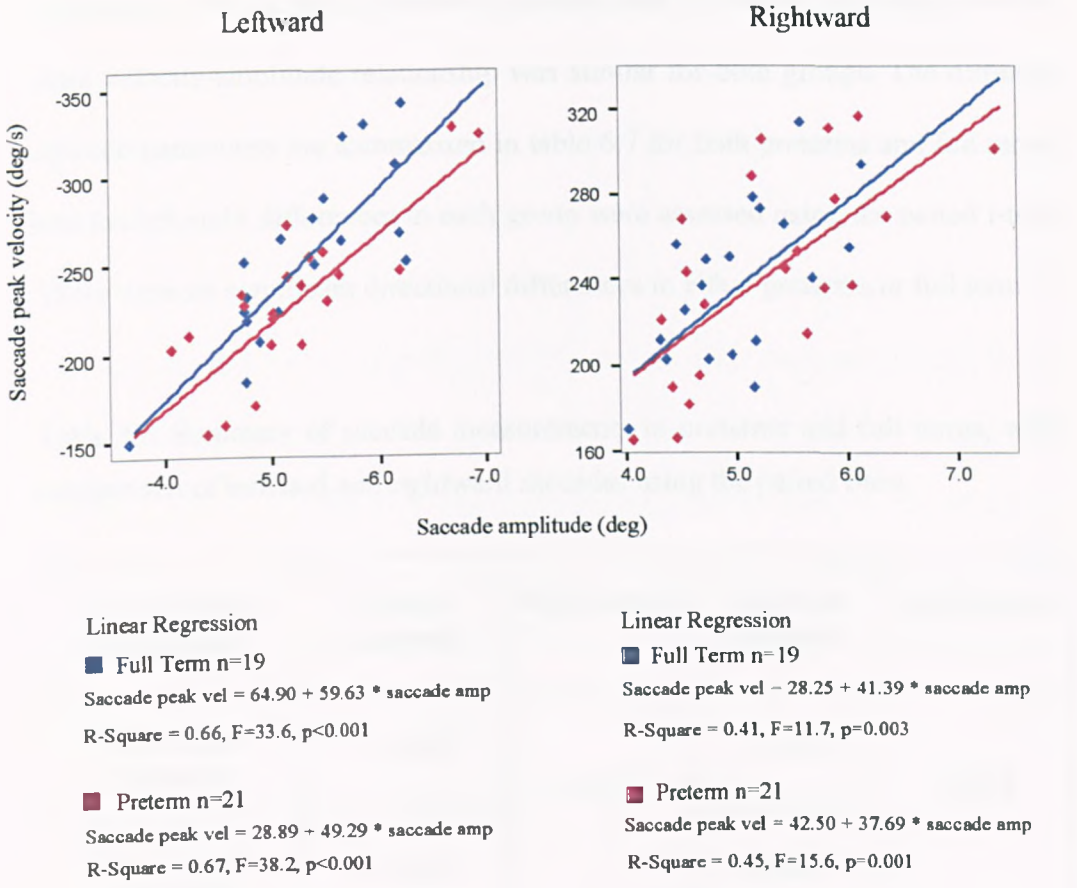


Figure 6.5 Peak velocity vs. saccade amplitude in preterms and full terms for both leftward and rightward saccades

As expected, the peak velocity and amplitude were significantly correlated in both groups for both leftward and rightward saccades demonstrating the normal main sequence relationship. As noted earlier when peak velocities were compared, it can be seen in Figure 6.5 that preterm saccades, particularly those that were hypermetric, were slightly slower than full terms. Statistical comparison of the regressions (Krzanowski, 1998) however revealed no significant difference between the regression coefficient (Leftward and

Rightward: F=4.12, p>0.1) between preterms and full terms, indicating that the peak velocity-amplitude relationship was similar for both groups. The different saccade parameters are summarised in table 6.7 for both preterms and full terms and the left-right differences in each group were assessed using the paired t-test. There were no significant directional differences in either preterms or full terms.

Table 6.7 Summary of saccade measurements in preterms and full terms, with comparison of leftward and rightward saccades using the paired t-test

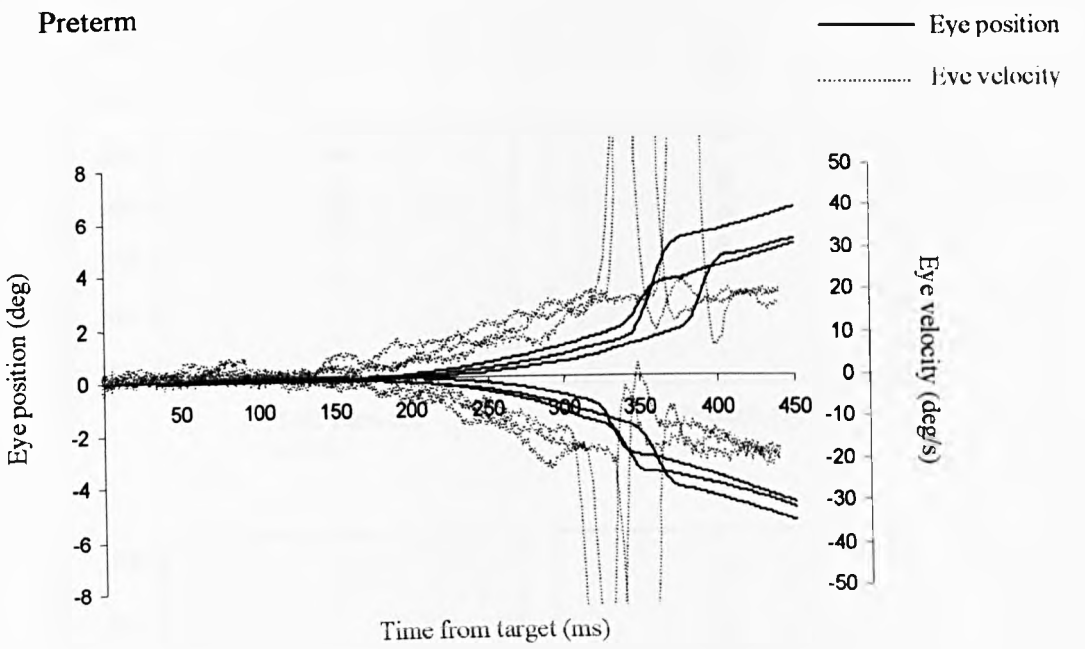
Eye movement measurement	Preterm mean±sd	Significance	Full term mean±sd	Significance
Saccade gain leftward	1.1±0.2	p=0.7	1.1±0.1	p=0.2
Saccade gain rightward	1.1±0.2		1.0±0.1	
Saccade latency leftward	206.2±43.3	p=0.6	200.1±30.0	p=0.3
Saccade latency rightward	210.4±37.8		204.8±33.5	
Saccade duration leftward	45.8±6.9	p=0.4	42.9±4.5	p=0.8
Saccade duration rightward	44.3±5.7		42.8±3.9	
Peak velocity leftward	-220.9±44.1	p=0.1	-254.5±49.8	p=0.2
Peak velocity rightward	243.0±41.1		238.2±37.6	

6.3 Control of smooth pursuit

The distribution of the measurements for latency, acceleration and velocity were assessed for preterms and full terms using the Kolmogorov-Smirnov test and found to be normally distributed (Appendix 2.3).

In a similar manner to saccades, smooth pursuit was analysed separately for leftward and rightward pursuit. An example of the pursuit traces for a preterm and full term subject are provided in Figure 6.6. Pursuit latency was longer in PTs (leftward: 219.2±33.2ms, rightward: 203.3±29.8ms; mean±sd) than FTs (leftward: 204.5±31.8ms, rightward: 180.6±27.4ms) but only reached statistical significance for pursuit to the right (L: t=-1.4, p=0.17; R: t=-2.5, p=0.02). The distribution of latencies for preterms and full terms are presented in Figure 6.7.

The mean acceleration of pursuit was also similar for both PT (leftward: -204.9±54.4deg/s/s, rightward: 202.2±69.9deg/s/s; mean±sd) and FT (leftward: -197.3±21.6deg/s/s, rightward: 200.5±90.1deg/s/s; L: t=0.6, p=0.6; R: t=-0.07, p=0.9) with neither difference being statistically significant.



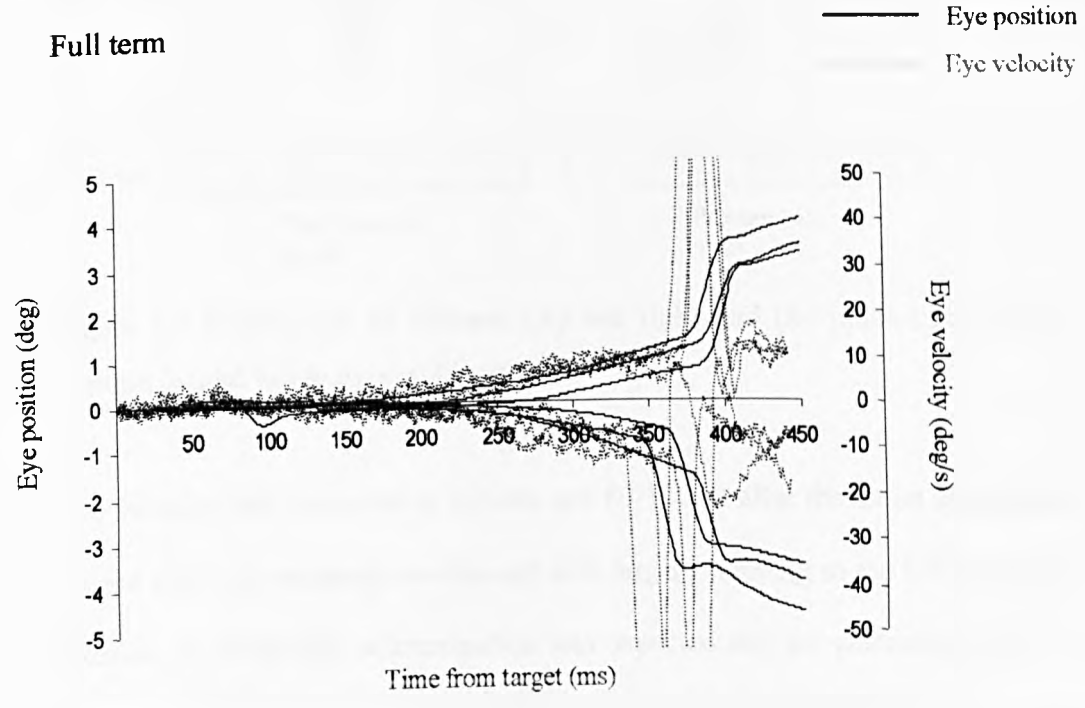


Figure 6.6 Examples of 3 pursuit traces (leftward and rightward) showing the eye position and velocity in a single preterm (top) and full term (bottom) subject.

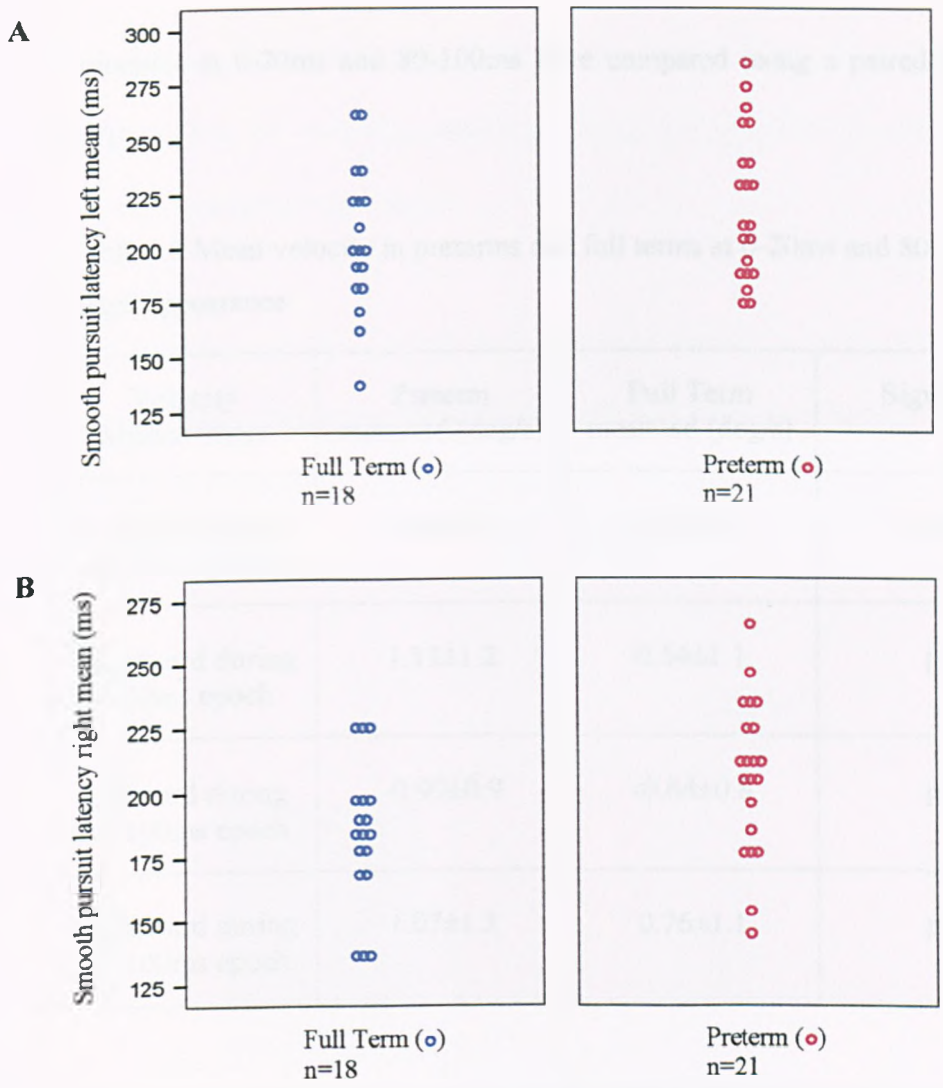


Figure 6.7 Distribution of leftward (A) and rightward (B) pursuit latencies in preterm (o) and full term (o) subjects

Eye velocity was measured at 0-20ms and 80-100ms after the target appearance. As the task was randomly interleaved with targets stepping to the left or right of fixation, no prediction or anticipation was expected and the velocities should be close to zero (table 6.8). There were no significant differences in velocity between preterms or full terms at either epoch. To assess if there was any indication of acceleration up to 100ms after the appearance of the target, the

velocities at 0-20ms and 80-100ms were compared using a paired t-test (table 6.9).

Table 6.8 Mean velocity in preterms and full terms at 0-20ms and 80-100ms after target appearance

Velocity Measurement	Preterm mean±sd (deg/s)	Full Term mean±sd (deg/s)	Significance
Leftward during 0-20ms epoch	-0.68±1.6	-0.21±1.1	p=0.3
Rightward during 0-20ms epoch	1.13±1.2	0.54±1.1	p=0.1
Leftward during 80-100ms epoch	-0.99±0.9	-0.64±0.8	p=0.2
Rightward during 80-100ms epoch	1.07±1.3	0.76±1.1	p=0.4

Table 6.9 Comparison of velocities in PT and FT between 0-20ms and 80-100ms after target appearance

Saccade Direction	Difference in velocities between epochs (0-20ms and 80-100ms)	
	Preterm mean±sd (significance)	Full Term mean±sd (significance)
Leftward	0.31±1.4 (p=0.3)	0.43±0.6 (p=0.01)
Rightward	0.06±1.2 (p=0.8)	0.22±0.9 (p=0.3)

The velocities were also measured at 80-100ms after the appearance of the target (at the end of the open loop period) and again during a 20ms epoch centred over the maximum slow eye velocity.

The velocities at the end of the open loop period were slightly higher for preterms than full terms for both leftward and rightward pursuit (figure 6.8), though the difference was not statistically significant (leftward: t=1.4, p=0.2; rightward: t=-1.1, p=0.3).

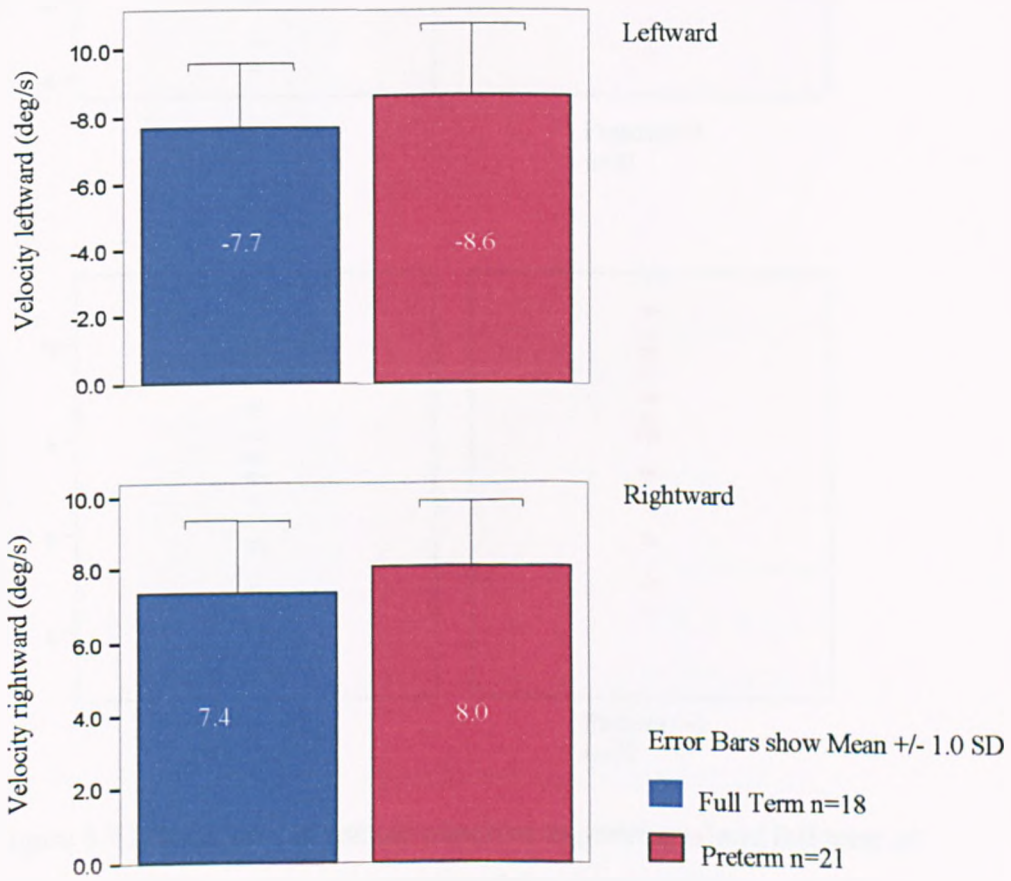


Figure 6.8 Mean pursuit velocity 80-100ms after appearance of the target (end of open loop) in preterms and full terms

There was a large amount of variability for both groups (leftward range PT: -4.6 to -13.4deg/s; FT: -4.3 to -11.9deg/s; rightward range PT: 4.4 to 10.6deg/s; FT: 3.8 to 10.9deg/s; figure 6.9)

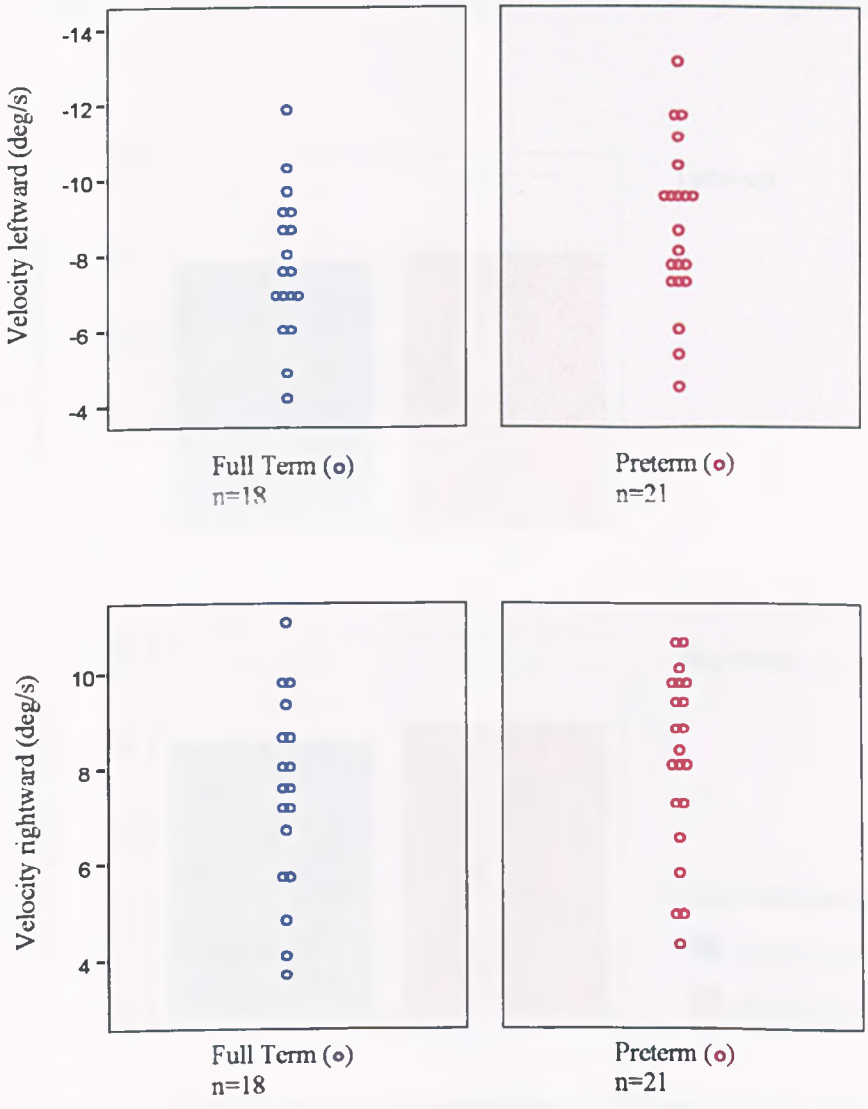


Figure 6.9 Distribution of pursuit velocities in preterm (o) and full term (o) subjects at 80-100ms after appearance of the target (end of open loop)

There were also no statistically significant differences (leftward: t=0.4, p=0.7; rightward: t=-0.7, p=0.5) in the maximum slow eye velocity between preterms and full terms (figure 6.10), but again there was considerable variability within the groups (leftward range PT: -4.9 to -21.8deg/s; FT: -7.6 to -21.7deg/s; rightward range PT: 6.9 to 22.7deg/s; FT: 6.3 to 20.8deg/s; figure 6.11).

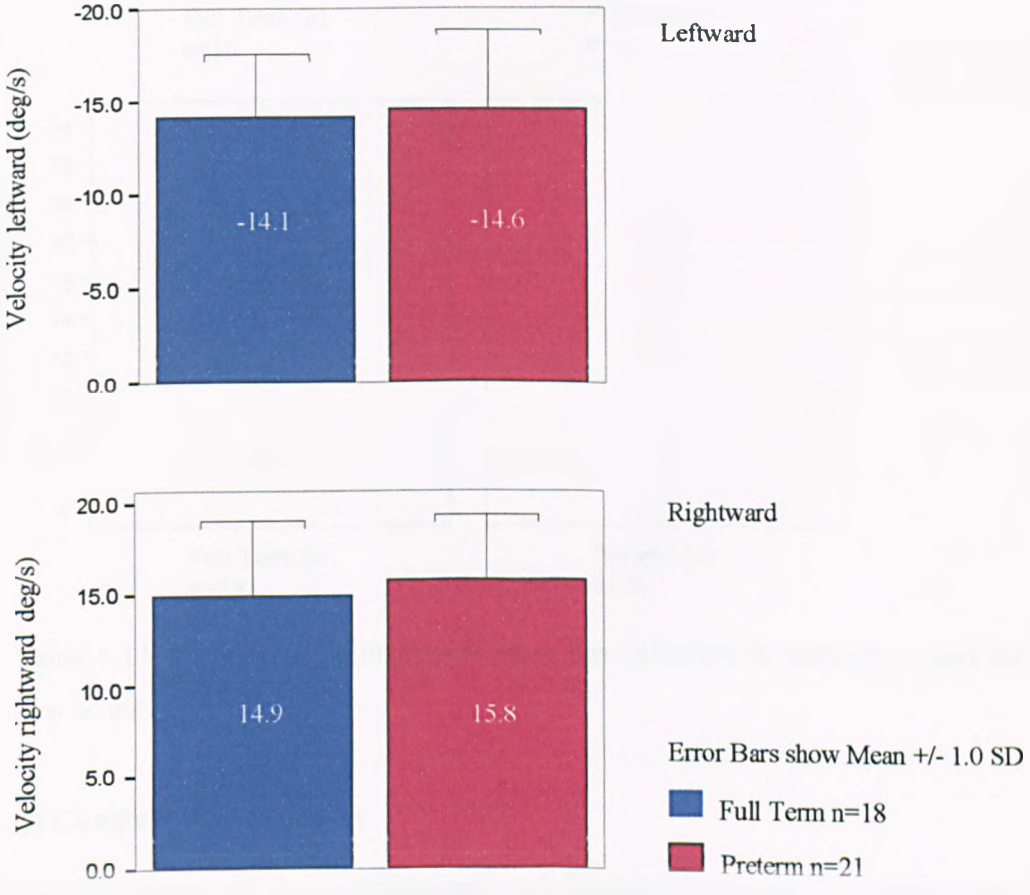


Figure 6.10 Maximum slow eye velocities in preterms and full terms

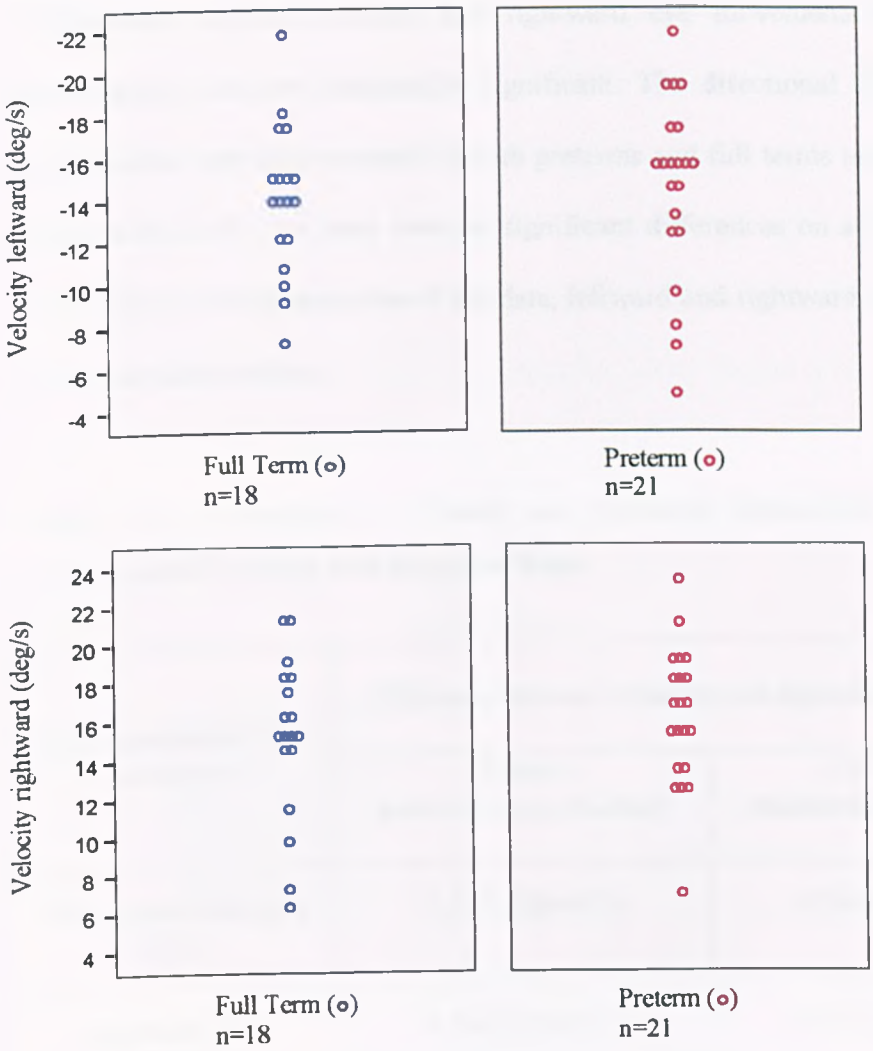


Figure 6.11 Distribution of maximum slow eye velocities in preterm (o) and full term (o) subjects

6.4 Control of antisaccades

The distribution of the measurements of directional error rate, rejection rate, latency of the antisaccade errors, percentage of express saccades, antisaccade error correction rate and latency of the antisaccade were assessed for preterms and full terms using the Kolmogorov-Smirnov test and found to be normally distributed (Appendix 2.4).

Differences between leftward and rightward eye movements for standard prosaccades were not statistically significant. The directional differences for antisaccades were also assessed in both preterms and full terms using the paired t-test (table 6.10). As there were no significant differences on any measure, to ease analysis and presentation of the data, leftward and rightward measurements were analysed together.

Table 6.10 Comparison of leftward and rightward antisaccade measures in preterms and full terms with the paired t-test

Measurement of eye movement	Difference between leftward and rightward antisaccades	
	Preterm mean±sd (significance)	Full Term mean±sd (significance)
Directional error rate (%)	1.1±4.0 (p=0.1)	0.9±4.6 (p=0.3)
Rejection rate (%)	0.5±2.6 (p=0.2)	0.8±3.0 (p=0.1)
Latency of antisaccade error (ms)	4.4±15.9 (p=0.1)	3.6±15.4 (p=0.2)
Proportion of express saccades (%)	1.1±5.1 (p=0.2)	0.3±2.8 (p=0.5)
Antisaccade error correction rate (%)	0.6±4.6 (p=0.5)	1.1±3.9 (p=0.1)
Latency of antisaccade (ms)	5.6±33.4 (p=0.3)	7.0±28.4 (p=0.2)

The antisaccade directional error rate was calculated for all valid trials where eye movements were elicited and where blinks did not obscure the direction of the saccade. The number of trials that had to be rejected was not significantly different between the two groups (PT: 9.1±6.8%, FT: 9.1±6.9%, mean±sd; t=0.05, p=1.0). The percentage of antisaccade directional errors was significantly higher (t=-4.5, p<0.001) for preterms than full terms (figure 6.12), with a range of 33.7 to 100% (PT) and 20.0 to 91.8% (FT, figure 6.13).

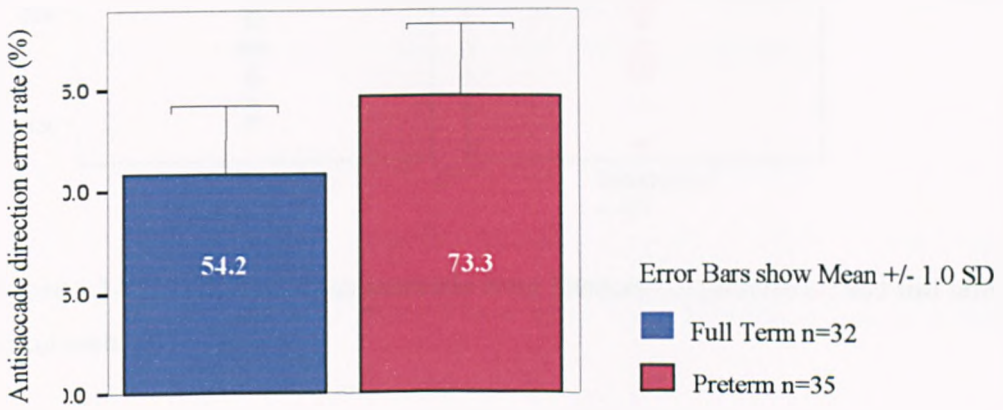


Figure 6.12 Percentage of antisaccade directional errors in preterms and full terms

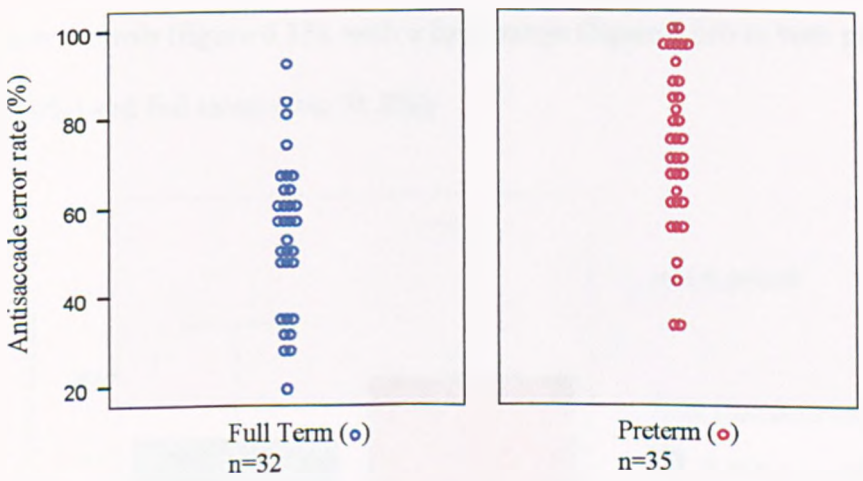


Figure 6.13 Distribution of antisaccade directional error rates (%) in preterm (o) and full term (o) subjects

The mean latency of the antisaccade errors was shorter for the preterm group (197.2±26.4ms, mean±sd) than the full term group (212.2±38.1ms, mean±sd; t=1.9, p=0.065), with a range (mean over the 96 trials) of 140.9 to 255.4ms (PT) and 149.8 to 298.1ms (FT, figure 6.14).

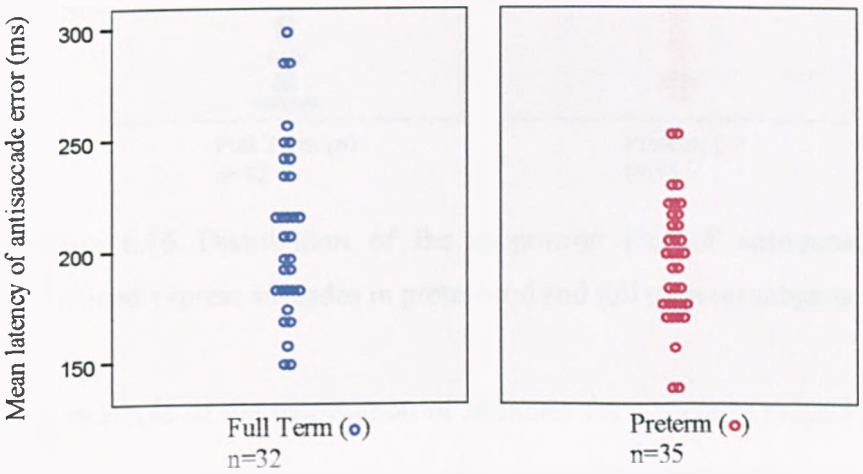


Figure 6.14 Distribution of antisaccade error latencies in preterm (o) and full term (o) subjects

Examination of the antisaccade error latencies in individual subjects revealed that preterms had a higher proportion of express saccades (90-140ms) than the full term controls (figure 6.15), with a large range (figure 6.16) in both preterms (0 to 80.0%) and full terms (0 to 51.8%).

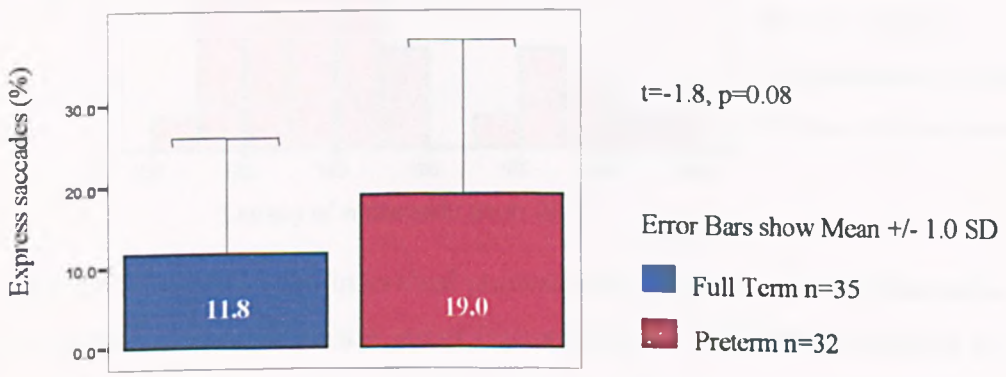


Figure 6.15 Percentage of express antisaccade errors in preterms and full terms

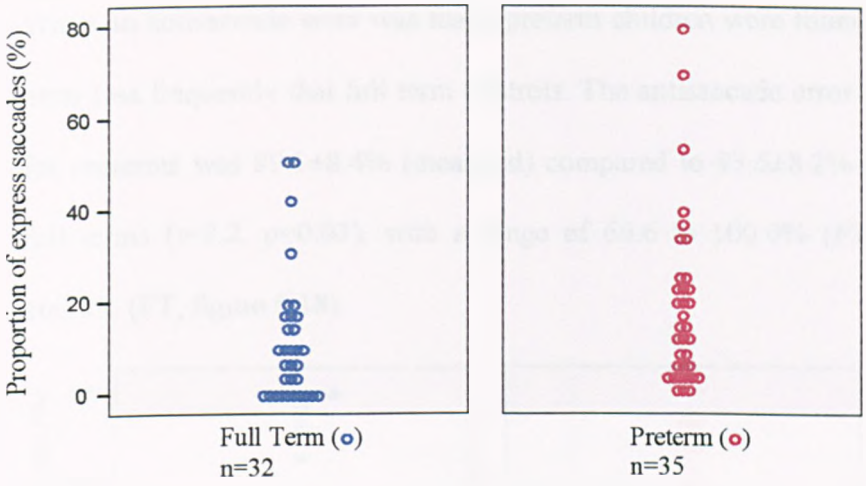


Figure 6.16 Distribution of the proportion (%) of antisaccade errors that contained express saccades in preterm (o) and full term (o) subjects

An example of the distribution of latencies for a preterm subject is provided in figure 6.17, which demonstrates the typical proportion of express antisaccade errors and the bimodal distribution that is often noted in when express saccades are generated (Fischer & Ramsperger, 1984).

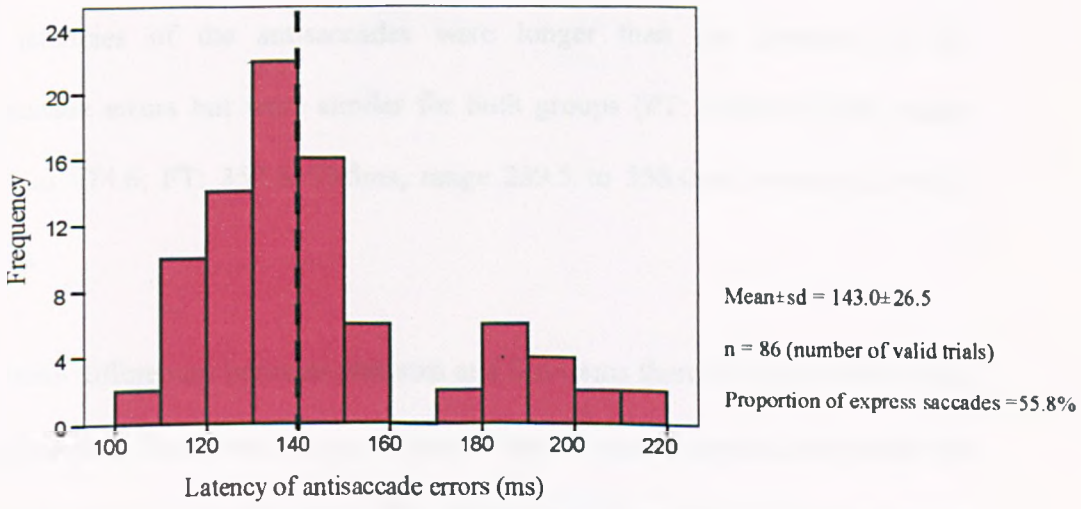


Figure 6.17 Example of an individual preterm subject showing the distribution of the latencies of the antisaccade errors (saccades to the left of the dotted line are express saccades)

When an antisaccade error was made preterm children were found to correct the error less frequently that full term controls. The antisaccade error correction rate for preterms was 89.1±8.4% (mean±sd) compared to 93.6±8.2% (mean±sd) for full terms (t=2.2, p=0.03), with a range of 66.6 to 100.0% (PT) and 72.4 to 100.0% (FT, figure 6.18).

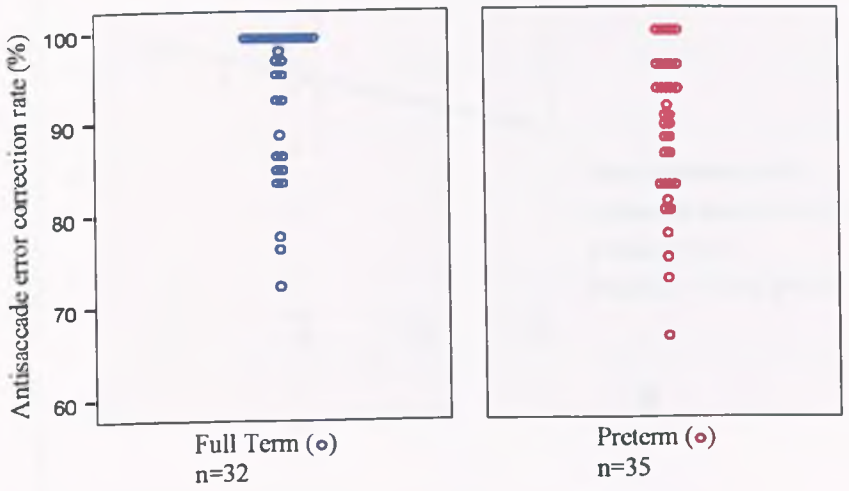


Figure 6.18 Distribution of the antisaccade error correction rate in preterm (o) and full term (o) subjects

The latencies of the antisaccades were longer than the latencies of the antisaccade errors but were similar for both groups (PT: 358.1±54.9ms, range 223.3 to 474.6; FT: 352.6±73.5ms, range 239.5 to 558.0ms, mean±sd; t=-0.3, p=0.7).

The main differences between preterms and full terms therefore were in the areas of antisaccade directional error rate, percentage of express antisaccade errors and antisaccade error correction rate. To determine if these areas were associated with the degree of prematurity, scatter plots with linear regression were generated and Pearson's test used to assess the presence of any correlation. No

significant correlations were present (figure 6.19). Additionally, using linear regression, GA was not found to be predictive of the antisaccade directional error rate (F=0.815, p=0.4), the percentage of express antisaccade errors (F=0.322, p=0.6) or the antisaccade error correction rate (F=0.064, p=0.8).

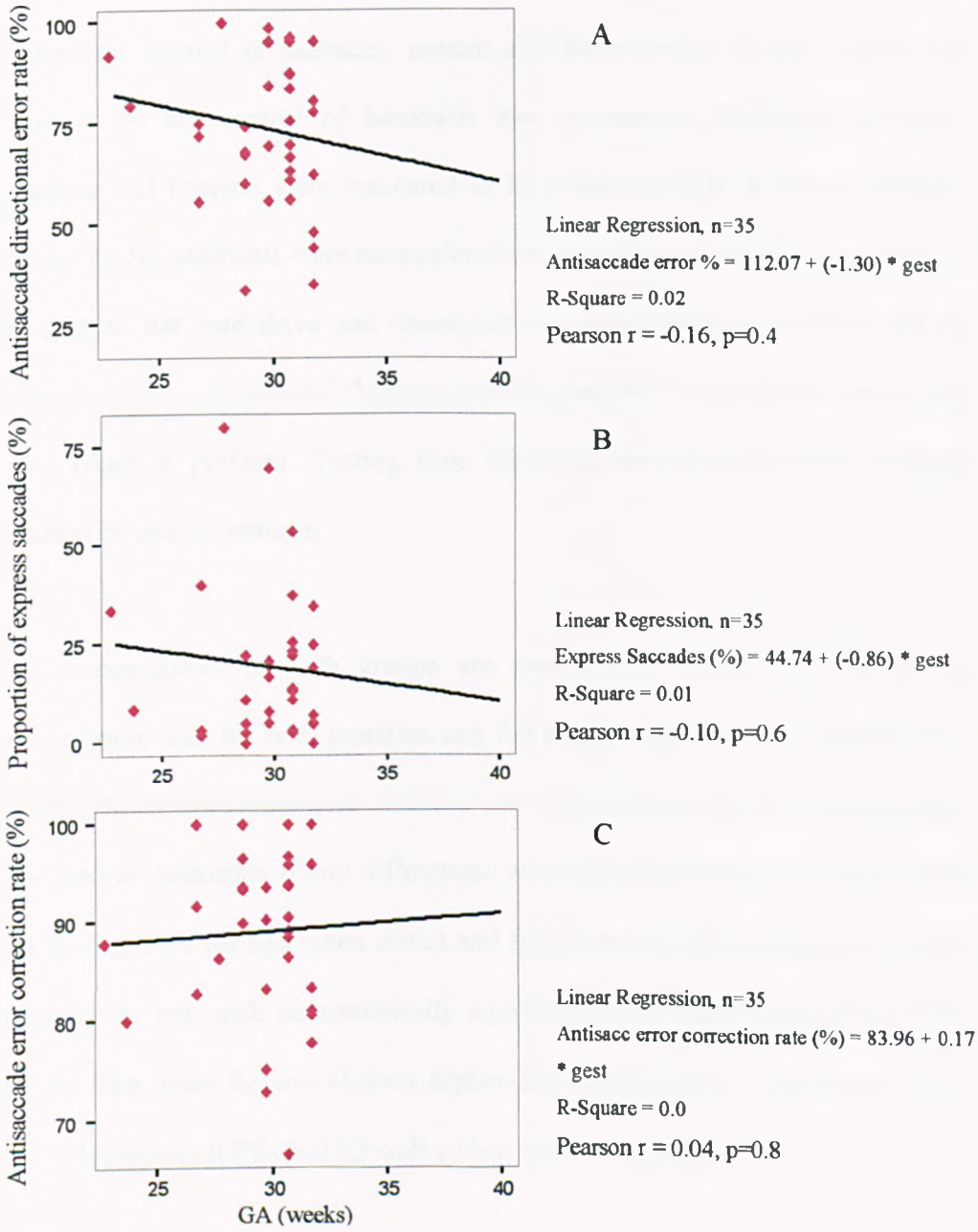


Figure 6.19 Relationship between GA and error rate (A), proportion of express saccades (B) and antisaccade error correction rate (C)

CHAPTER 7: Binocular co-ordination of saccades and control of vergence and fixation in children born preterm vs. full term (Experiment 2)

In the previous chapter the emphasis was on the assessment of monocular oculomotor control of saccades, pursuit and antisaccades. In this chapter the focus is on the control of binocular eye movements. Binocular saccades, vergence and fixation were measured in 15 preterm and 14 full term children (Group 2). No problems were encountered during testing or with the recording of the data to the hard drive and measurements were therefore available for all subjects. Both preterm and full term subjects coped well with all of the tasks they were asked to perform. Testing time including rest breaks typically ranged between 50 and 60 minutes.

The demographics of both groups are presented in Table 7.1. All of the demographic data for both preterms and full terms were normally distributed as determined by the Kolmogorov-Smirnov test (Appendix 2.5). An unpaired t-test was used to determine if any differences were present between the preterm and full term groups for age when tested and full scale IQ. Both groups were well matched for age with no statistically significant differences present ($t=-0.875$, $p=0.4$). The mean IQ was slightly higher in full terms than preterms ($t=2.418$, $p=0.02$), though all PTs had IQ well within the normal range.

Table 7.1 Demographics of preterm and full term children recruited for Experiment 2

	Preterm Group	Full Term Group
Number of subjects	15	14
Mean age when tested (months) and range	131.9 120-143	129.5 120-142
Mean full scale IQ and range	99 86-108	106 96-121
Mean GA (weeks) and range	29.9 23-32	37+
Mean birth weight (g) and range	1468 622-2300	N/A

7.1 Statistical analysis

The normality of the distribution of the binocular co-ordination of saccades, vergence and fixation data was determined statistically using the Kolmogorov-Smirnov test. All data was normally distributed for both preterm term and full term groups. As the data was both continuous and normally distributed the unpaired t-test was used to compare the means. Levene's test was used to check for equality of variance between the means and depending on the result, the appropriate p value was recorded.

7.2 Binocular co-ordination of saccades

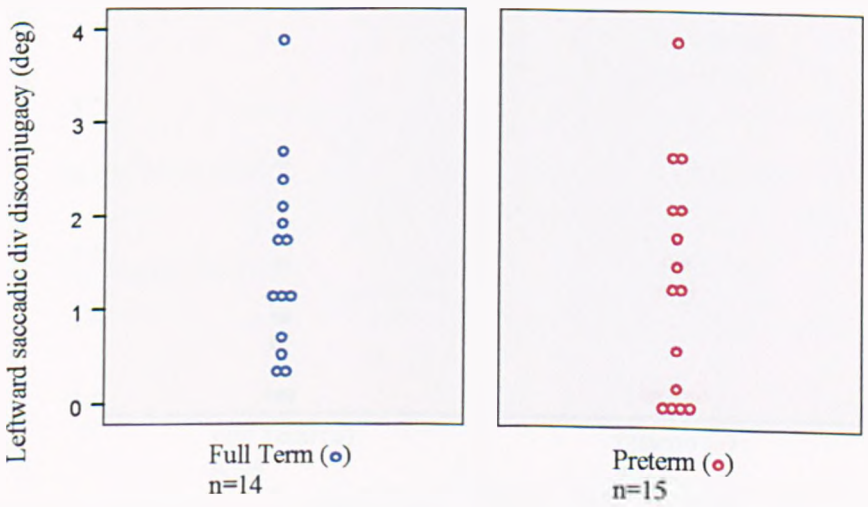
In common with previous research (Kapoula et al., 1997, Yang & Kapoula, 2003), saccades were analysed separately for leftward and rightward saccades due to differences that may occur due to the direction of the eye movement. The distribution of measurements of the amplitude of saccade disconjugacy (convergent and divergent) and the post-saccadic drift at 75ms and 150ms after the saccade offset (convergent and divergent) were assessed using the Kolmogorov-Smirnov test and found to be normally distributed (Appendix 2.6) for both preterms and full terms.

A comparison of the saccadic disconjugacy between preterms and full terms is summarised in Table 7.2. The mean amplitude of convergent saccadic disconjugacy was similar for preterms and full terms for both leftward and rightward saccades. There was also little difference in divergent saccadic disconjugacy between the groups for either leftward or rightward saccades. Preterms showed more variation for leftward and rightward convergent (figure 7.1) and leftward and rightward divergent (figure 7.2) saccadic disconjugacy than full terms as reflected by the larger standard deviations.

Table 7.2 Comparison of convergent and divergent saccadic disconjugacy for leftward and rightward saccades between preterms and full terms

Type of disconjugacy and saccade direction	Amount of disconjugacy (degrees)		Significance
	Preterms mean±sd (range)	Full terms mean±sd (range)	
Divergent saccadic disconjugacy (leftward)	1.3±1.2 (0 to 3.9)	1.6±1.0 (0.3 to 3.9)	p=0.6
Divergent saccadic disconjugacy (rightward)	1.2±1.1 (0 to 3.4)	1.0±0.9 (0 to 2.7)	p=0.6
Convergent saccadic disconjugacy (leftward)	1.0±1.2 (0 to 3.8)	0.8±0.8 (0 to 2.2)	p=0.6
Convergent saccadic disconjugacy (rightward)	1.1±1.3 (0 to 4.9)	1.2±1.0 (0 to 3.2)	p=0.8

A



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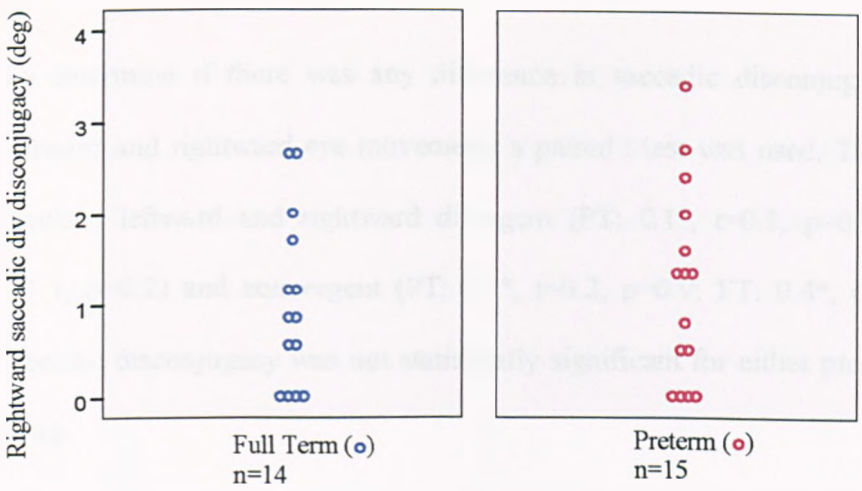
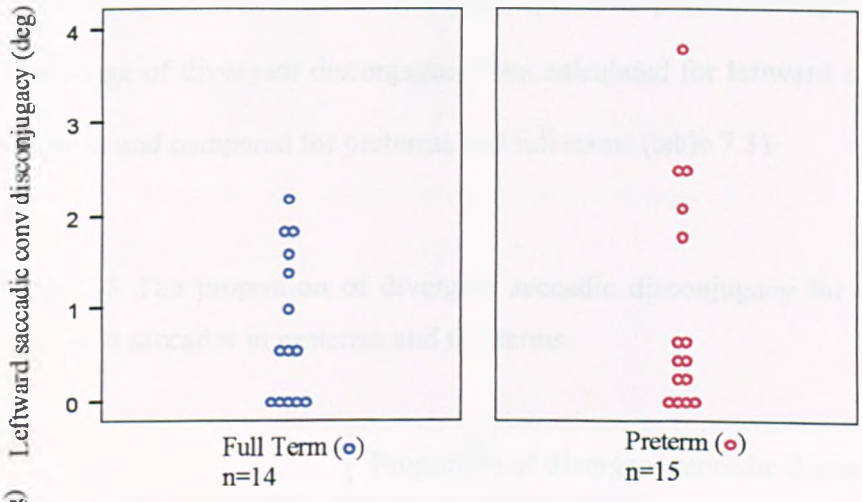


Figure 7.1 Distribution of leftward (A) and rightward (B) saccadic divergent disconjugacy in preterm (o) and full term (o) subjects

A



B

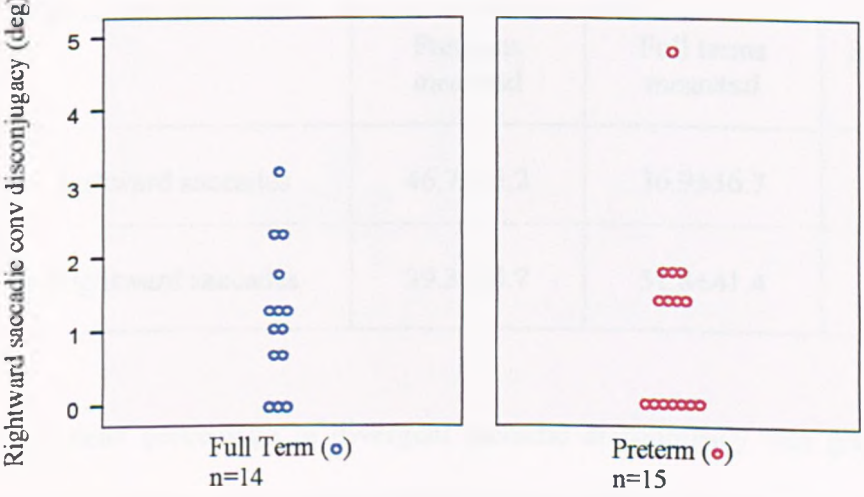


Figure 7.2 Distribution of the leftward (A) and rightward (B) saccadic convergent disconjugacy in preterm (o) and full term (o) subjects

To determine if there was any difference in saccadic disconjugacy between leftward and rightward eye movements a paired t-test was used. The difference between leftward and rightward divergent (PT: 0.1°, t=0.3, p=0.8; FT: 0.6°, t=1.4, p=0.2) and convergent (PT: 0.1°, t=0.2, p=0.9; FT: 0.4°, t=1.5, p=0.2) saccadic disconjugacy was not statistically significant for either preterms or full terms.

To examine the nature of the convergent and divergent saccadic disconjugacy in more detail, and determine if the disconjugacy was predominantly divergent, the percentage of divergent disconjugacy was calculated for leftward and rightward saccades and compared for preterms and full terms (table 7.3).

Table 7.3 The proportion of divergent saccadic disconjugacy for leftward and rightward saccades in preterms and full terms

Direction of saccades	Proportion of divergent saccadic disconjugacy (%)		
	Preterms mean±sd	Full terms mean±sd	Significance
Leftward saccades	46.7±45.2	36.9±36.7	p=0.5
Rightward saccades	39.3±44.7	51.8±41.4	p=0.4

The mean percentage of divergent saccadic disconjugacy was greater for full terms for rightward saccades only, though neither difference was statistically significant. Both preterms and full terms had a large amount of variability with a

large range of values (figure 7.3). The difference in the proportion of divergent disconjugacy between leftward and rightward saccades was not statistically significant for either preterms (7.4±75.1%; mean±sd, t=0.4, p=0.7) or full terms (14.9±61.4%; mean±sd, t=-0.9, p=0.4).

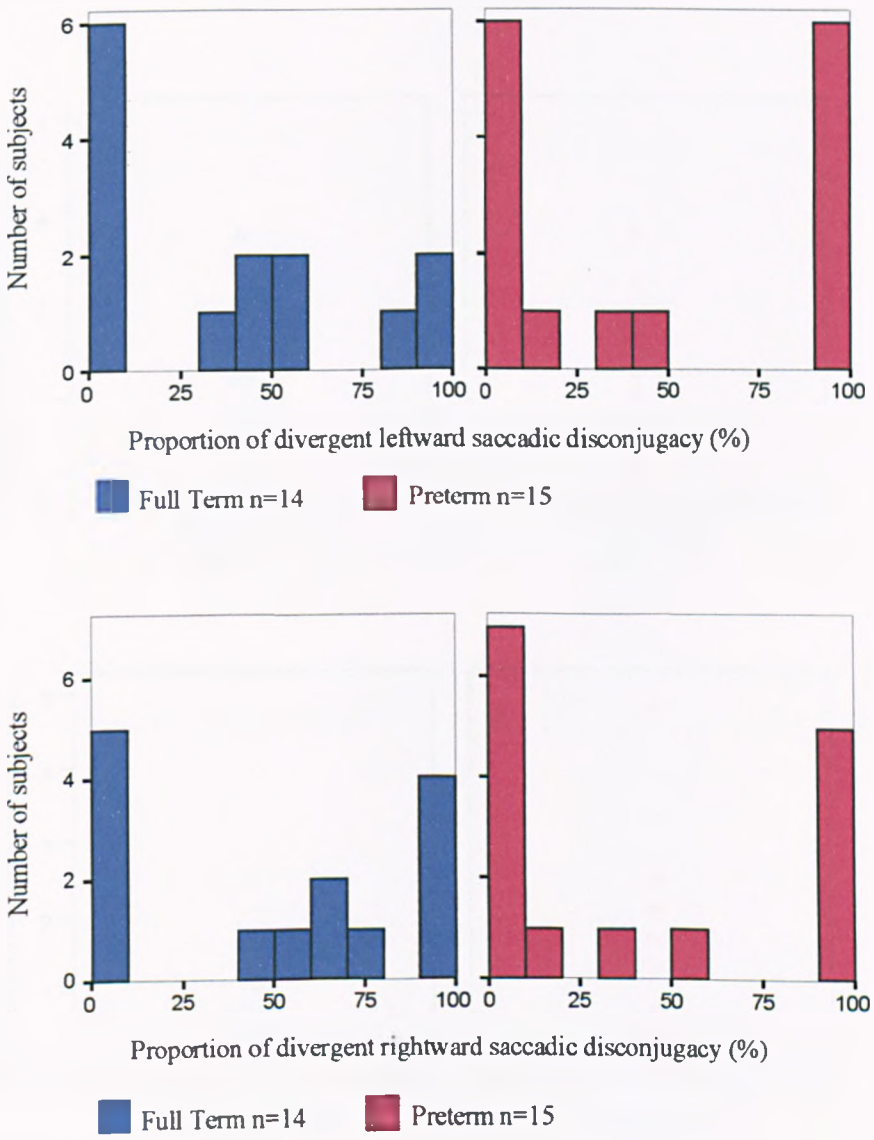
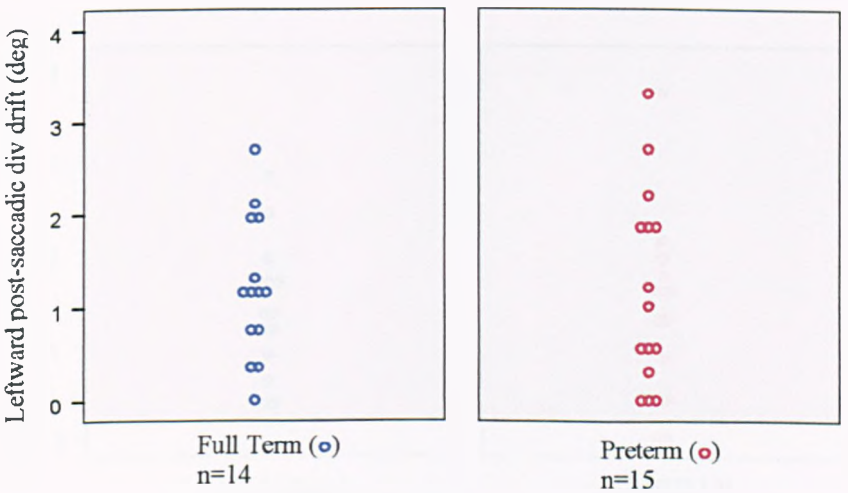
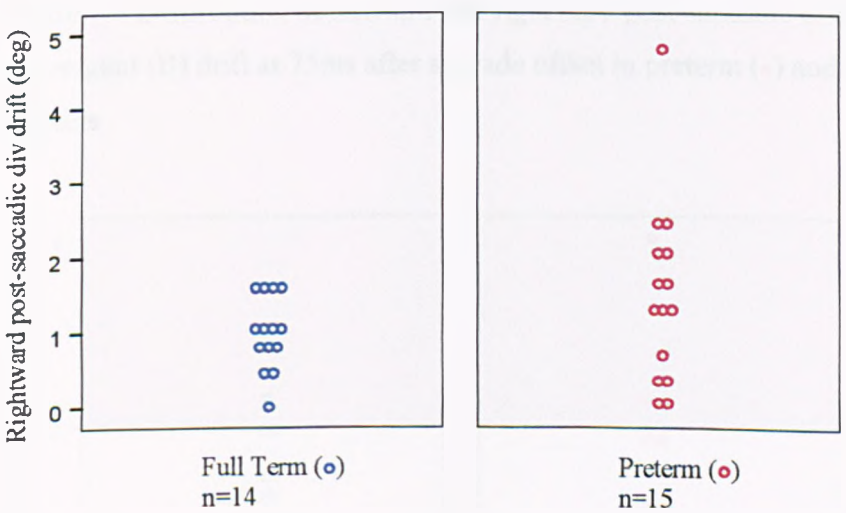


Figure 7.3 Distribution of the proportion of divergent saccadic disconjugacy during leftward and rightward saccades in preterms and full terms

The extent of disconjugacy after the saccade, referred to as post-saccadic drift was measured at 75ms and 150ms after the saccade offset for both leftward and rightward saccades. Data for individual preterm and full term subjects are presented graphically for both 75ms (figure 7.4) and 150ms (figure 7.5) after saccade offset.

A





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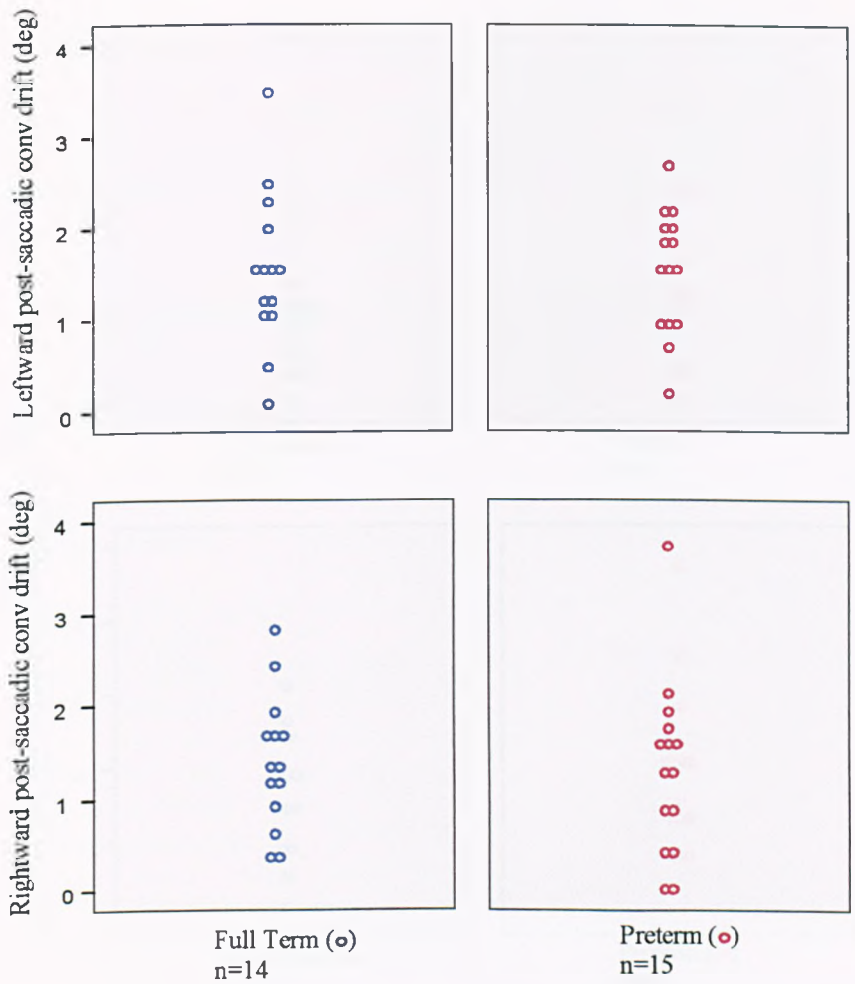
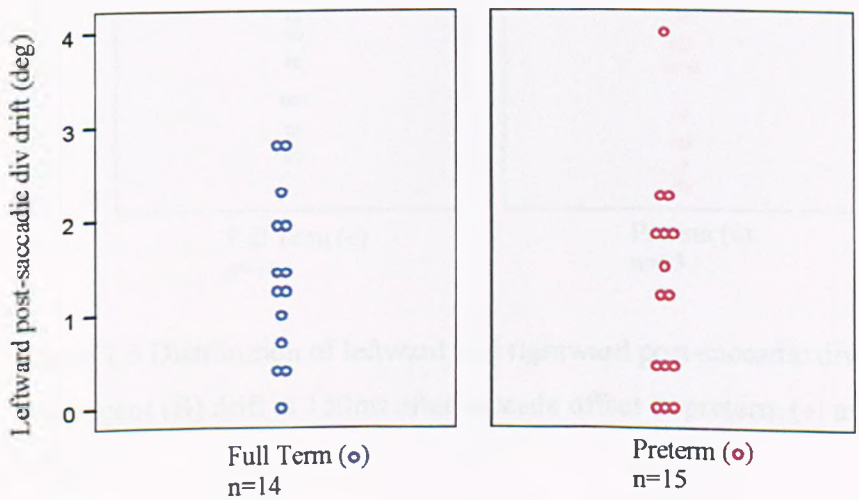
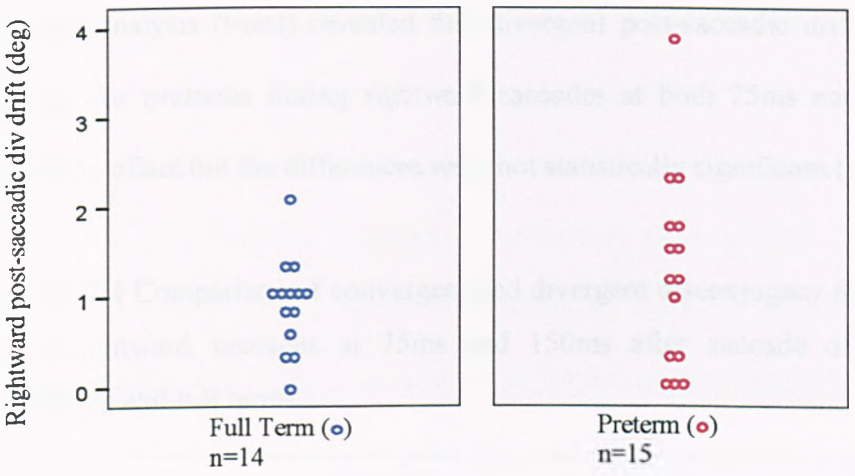


Figure 7.4 Distribution of leftward and rightward post-saccadic divergent (A) and convergent (B) drift at 75ms after saccade offset in preterm (o) and full term (o) subjects

A





B

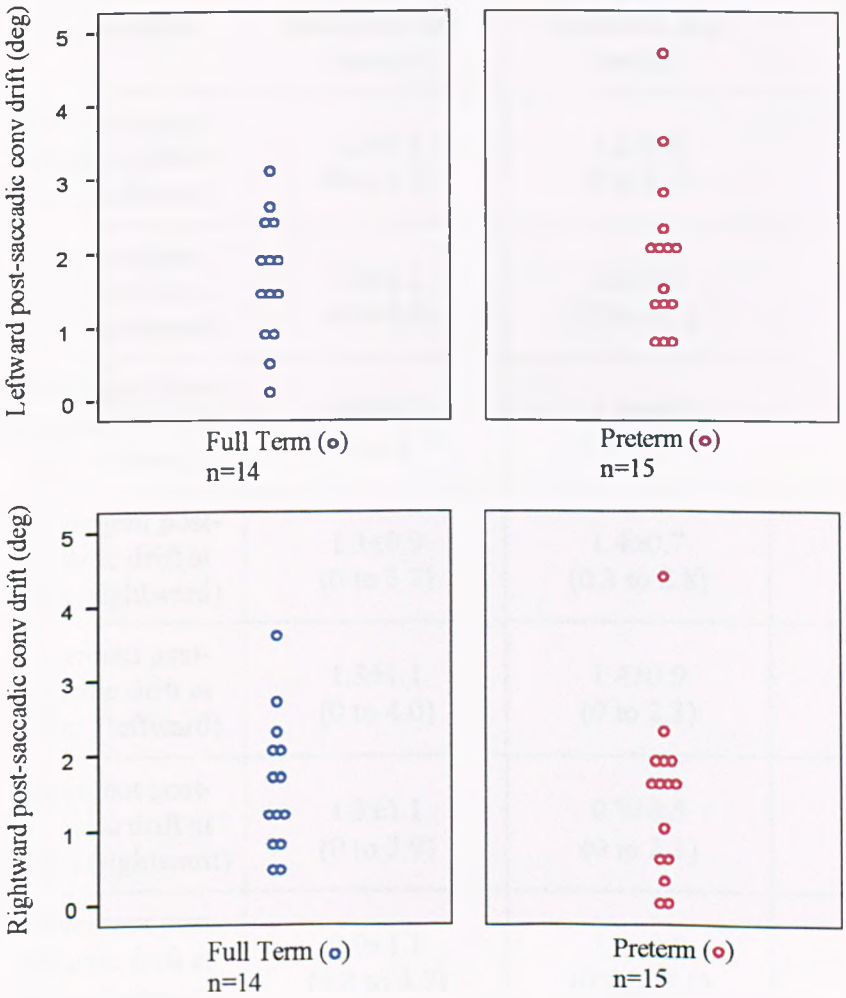


Figure 7.5 Distribution of leftward and rightward post-saccadic divergent (A) and convergent (B) drift at 150ms after saccade offset in preterm (o) and full term (o) subjects

Group analysis (t-test) revealed that divergent post-saccadic drift was slightly larger for preterms during rightward saccades at both 75ms and 150ms after saccade offset but the differences were not statistically significant (table 7.4).

Table 7.4 Comparison of convergent and divergent disconjugacy during leftward and rightward saccades at 75ms and 150ms after saccade offset, between preterms and full terms

Eye movement measurement	Preterm mean±sd, deg (range)	Full term mean±sd, deg (range)	Significance
Divergent post-saccadic drift at 75ms (leftward)	1.2±1.2 (0 to 3.3)	1.2±0.8 (0 to 2.7)	p=1.0
Divergent post-saccadic drift at 75ms (rightward)	1.5±1.2 (0 to 4.8)	1.0±0.5 (0 to 1.7)	p=0.2
Convergent post-saccadic drift at 75ms (leftward)	1.5±0.7 (0.2 to 2.7)	1.6±0.9 (0.1 to 3.5)	p=1.0
Convergent post-saccadic drift at 75ms (rightward)	1.3±0.9 (0 to 3.7)	1.4±0.7 (0.3 to 2.8)	p=0.8
Divergent post-saccadic drift at 150ms (leftward)	1.3±1.1 (0 to 4.0)	1.4±0.9 (0 to 2.8)	p=0.7
Divergent post-saccadic drift at 150ms (rightward)	1.3±1.1 (0 to 3.9)	0.9±0.5 (0 to 2.1)	p=0.3
Convergent post-saccadic drift at 150ms (leftward)	2.0±1.1 (0.8 to 4.7)	1.6±0.8 (0.1 to 3.1)	p=0.4
Convergent post-saccadic drift at 150ms (rightward)	1.4±1.1 (0 to 4.4)	1.6±0.9 (0.4 to 3.6)	p=0.7

To assess if there was any difference in post-saccadic drift between leftward and rightward saccades a paired t-test was used (table 7.5). At 75ms after saccade offset, the difference between leftward and rightward divergent post-saccadic drift and leftward and rightward convergent post-saccadic drift was not statistically significant for either preterms or full terms. However, at 150ms after saccade offset, the differences were larger for divergent post-saccadic drift in full terms (p=0.06) and convergent post-saccadic drift in preterms (p=0.05).

Table 7.5 Difference in post-saccadic drift between leftward and rightward saccades at 75ms and 150ms after target offset in preterms and full terms

Type of drift and time after target offset	Difference in mean post-saccadic drift between leftward and rightward saccades (degrees)			
	Preterm	Significance	Full term	Significance
Divergent drift 75ms after target offset	0.29	p=0.4	0.22	p=0.3
Convergent drift 75ms after target offset	0.27	p=0.3	0.19	p=0.5
Divergent drift 150ms after target offset	0.01	p=1.0	0.46	p=0.06
Convergent drift 150ms after target offset	0.54	p=0.05	0.04	p=0.9

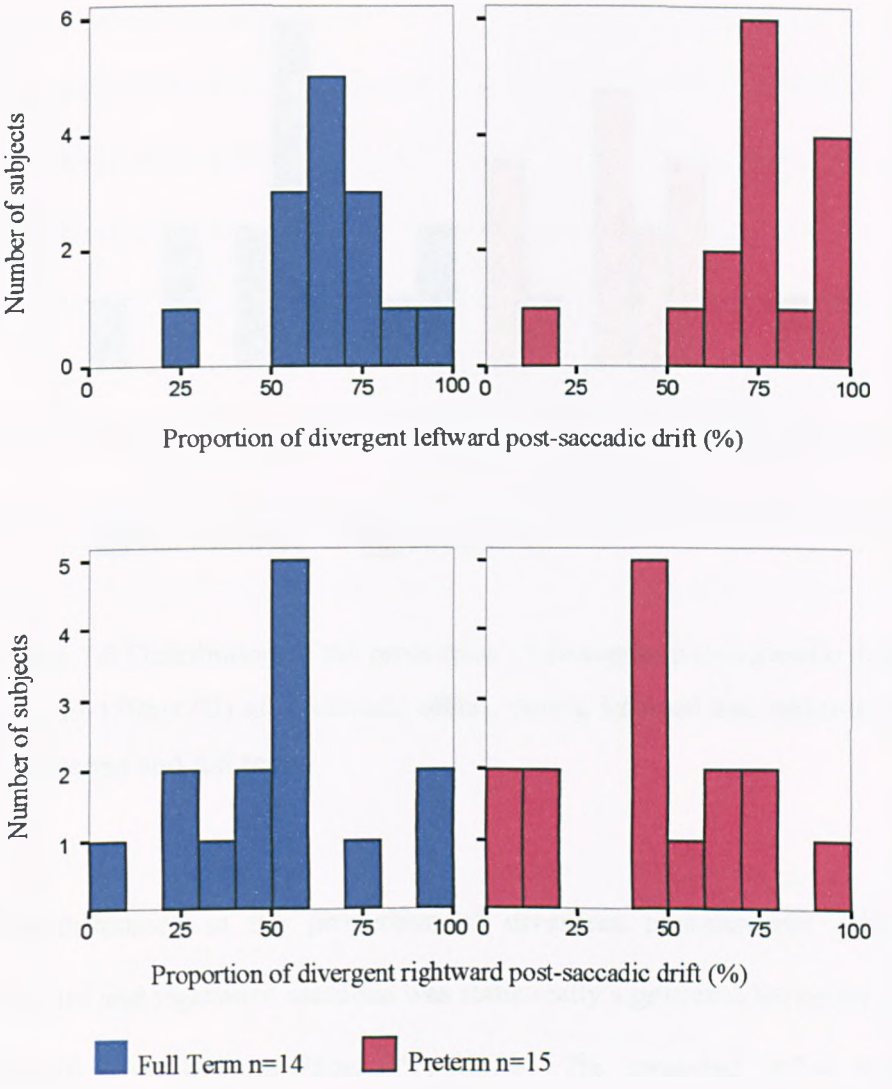
The nature of the convergent and divergent post-saccadic drift was examined in more detail to determine if the disconjugacy was predominantly divergent and if there were differences between the groups. The percentage of divergent post-saccadic drift was calculated for leftward and rightward saccades and compared for preterms and full terms (table 7.6).

Table 7.6 The proportion of divergent post-saccadic drift of leftward and rightward saccades in preterms and full terms

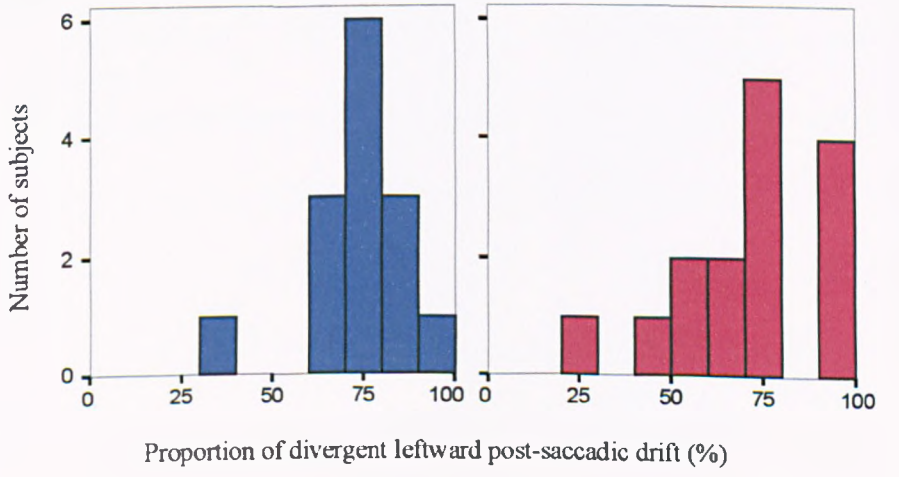
Direction of saccades and time after saccade offset	Proportion of divergent post-saccadic drift (%)		
	Preterms mean±sd	Full terms mean±sd	Significance
Leftward saccades at 75ms	76.6±21.4	66.1±17.9	p=0.2
Rightward saccades at 75ms	46.5±29.1	50.8±25.6	p=0.7
Leftward saccades at 150ms	71.9±20.2	73.0±15.0	p=0.9
Rightward saccades at 150ms	42.1±28.8	54.7±25.6	p=0.2

At both 75ms and 150ms after saccade offset for leftward and rightward saccades, full terms had more divergent post-saccadic drift than convergent. The proportion of divergent post-saccadic drift was not significantly different between preterms and full terms at either 75ms or 150ms after saccade offset. The variability between subjects for the proportion of divergent post-saccadic drift in preterms and full terms is illustrated in Figure 7.6.

A


Number of subjects
0
2
4
6
0
25
50
75
100
Proportion of divergent leftward post-saccadic drift (%)
Number of subjects
1
2
3
4
5
Proportion of divergent rightward post-saccadic drift (%)
Full Term n=14
Preterm n=15

B


Number of subjects
0
2
4
6
0
25
50
75
100
Proportion of divergent leftward post-saccadic drift (%)

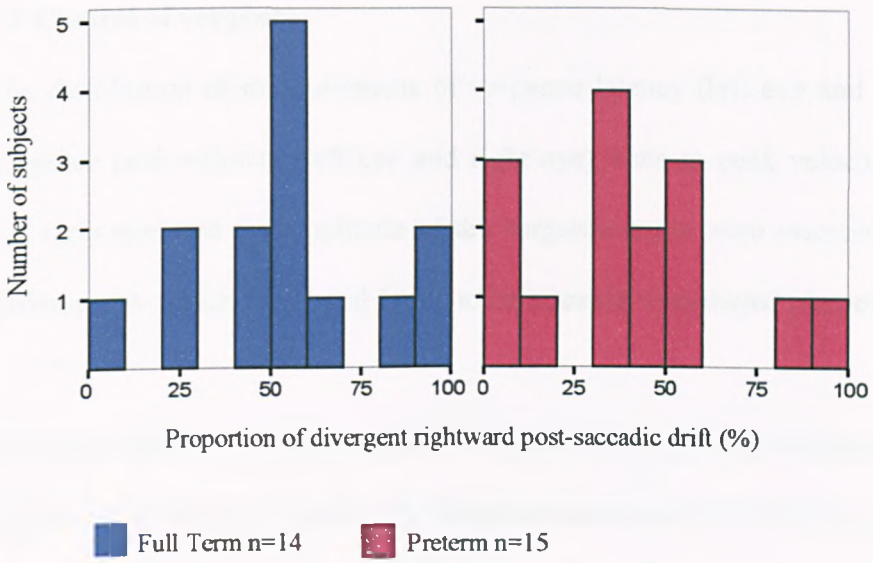


Figure 7.6 Distribution of the proportion of divergent post-saccadic drift at 75ms (A) and 150ms (B) after saccade offset, during leftward and rightward saccades in preterms and full terms

The difference in the proportion of divergent post-saccadic drift between leftward and rightward saccades was statistically significant for preterms, but not for full terms at both 75ms (PT: 30.1±47.7%, mean±sd, t=2.4, p=0.03; FT: 15.3±40.7, mean±sd, t=1.4, p=0.2) and 150ms (PT: 29.9±44.4%, mean±sd, t=2.6, p=0.02; FT: 18.2±38.8, mean±sd, t=1.8, p=0.1) after saccade offset.

7.3 Control of vergence

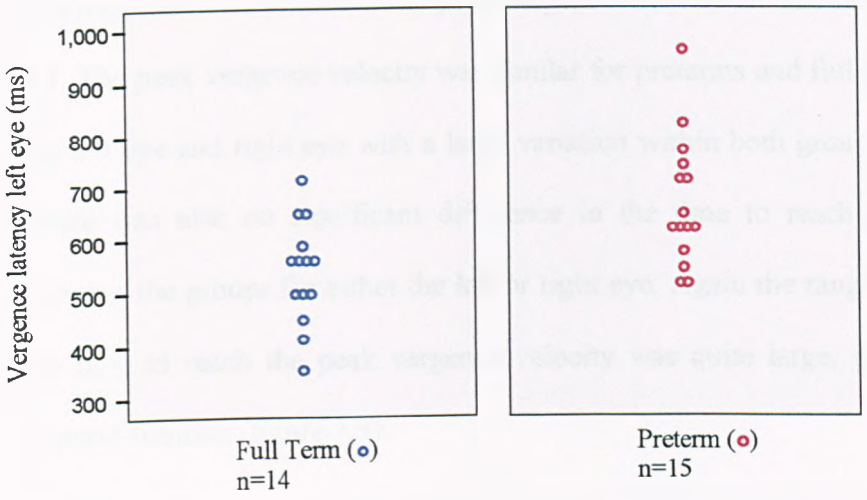
The distribution of measurements of vergence latency (left eye and right eye), vergence peak velocity (left eye and right eye), time to peak velocity (left eye and right eye) and the amplitude of the vergence angle were assessed using the Kolmogorov-Smirnov test and found to be normally distributed (Appendix 2.7)

The time taken to initiate vergence (vergence latency) was compared between preterms and full terms (table 7.7). Vergence latencies, for both left eye and right eye, were significantly longer in preterms than full terms. The variability of vergence latency was greater for preterms as indicated by the standard deviation and the distribution of latencies is illustrated in Figure 7.7.

Table 7.7 Comparison of vergence latency between preterms and full terms

Measurement	Preterm mean±sd (ms)	Full Term mean±sd (ms)	Significance
Vergence latency of left eye	664.6±122.9	539.8±97.4	p=0.006
Vergence latency of right eye	697.4±133.7	515.1±77.6	p<0.001

A



B

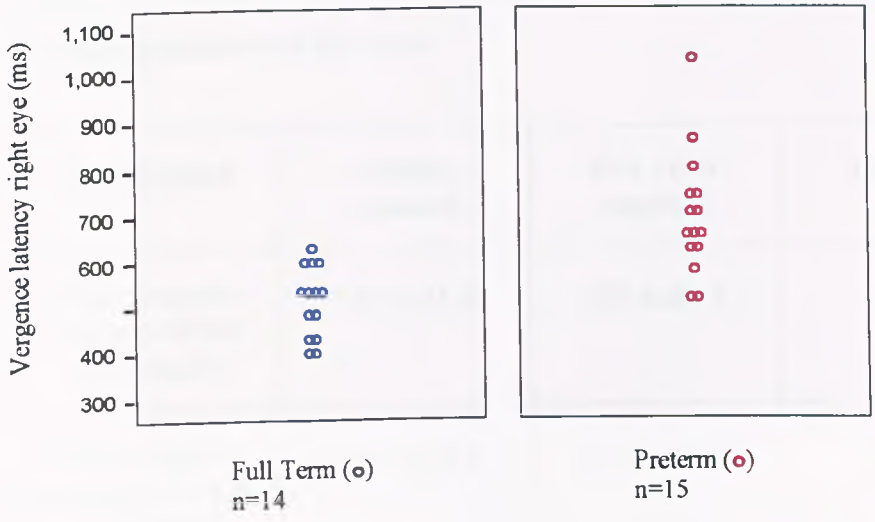


Figure 7.7 Distribution of vergence latency in the left eye (A) and right eye (B) in preterm (o) and full term (o) subjects

To assess if there was a difference in latency between the left eye and right eye, which could lead to difficulties in maintaining binocularity, a paired t-test was used. The interocular difference was larger for preterms (32.8±60.8ms, t= -2.1, p=0.055) than full terms (24.8±62.4ms, t= 1.5, p=0.2), though not statistically significant.

The measurements related to the peak vergence velocity are summarised in Table 7.8. The peak vergence velocity was similar for preterms and full terms for both the left eye and right eye with a large variation within both groups (figure 7.8). There was also no significant difference in the time to reach peak velocity between the groups for either the left or right eye. Again the range of values for the time to reach the peak vergence velocity was quite large, particularly for preterm subjects (figure 7.9).

Table 7.8 Comparison of peak vergence velocity and time to reach peak velocity between preterms and full terms

Measurement	Preterm mean±sd	Full Term mean±sd	Significance
Peak vergence velocity of left eye (deg/s)	198.3±55.3	209.8±69.4	p=0.6
Peak vergence velocity of right eye (deg/s)	-203.9±72.8	-171.6±60.6	p=0.2
Time to reach peak velocity of left eye (ms)	903.0±199.8	868.4±113.7	p=0.6
Time to reach peak velocity of right eye (ms)	824.9±163.8	910.8±166.8	p=0.2

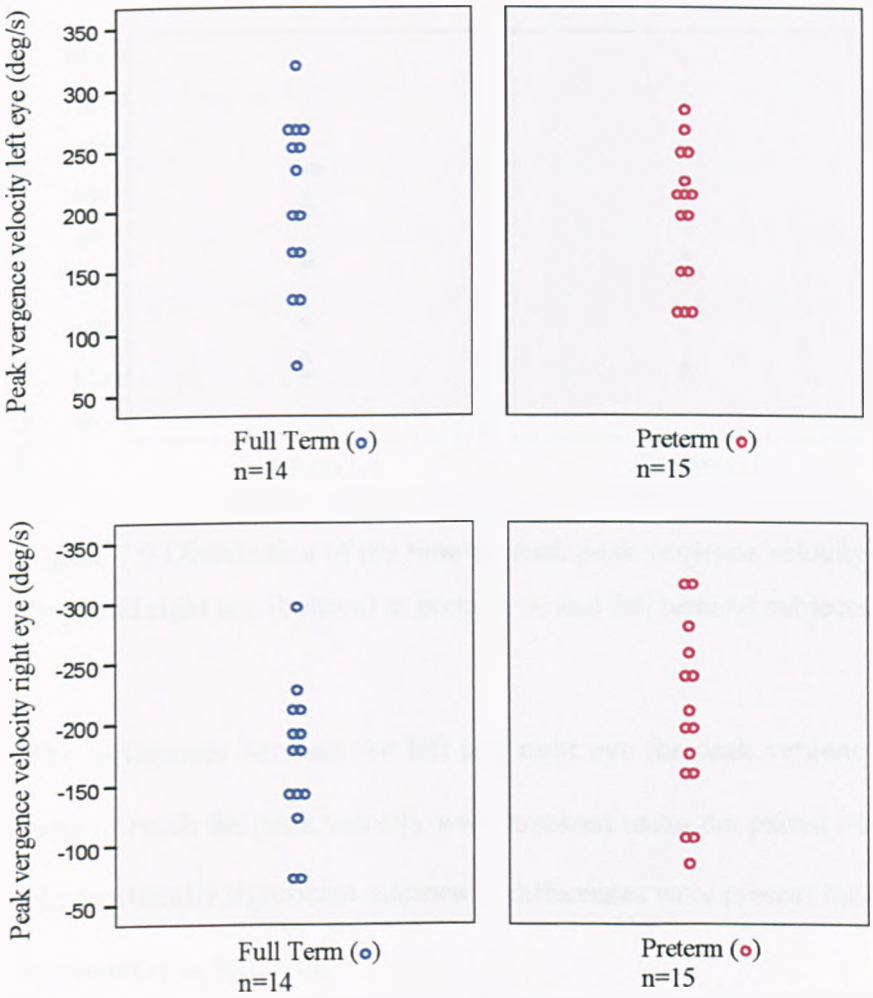
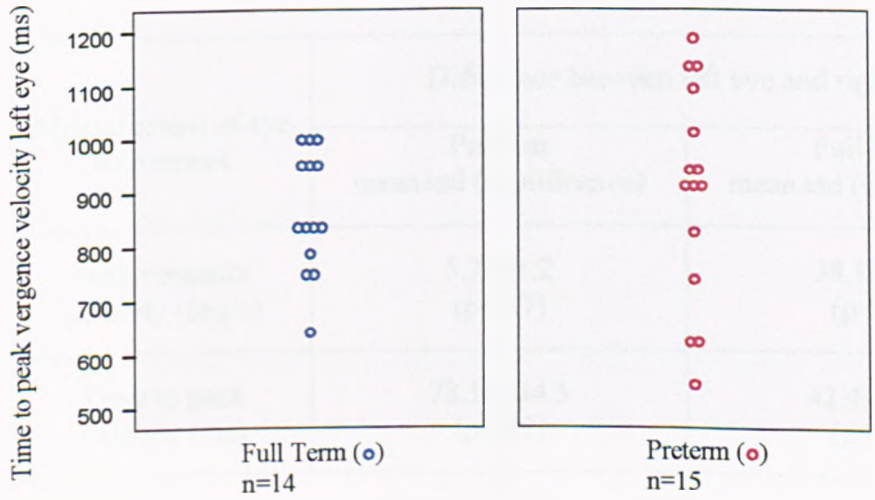


Figure 7.8 Distribution of peak vergence velocity in the left eye (top) and right eye (bottom) in preterm (o) and full term (o) subjects



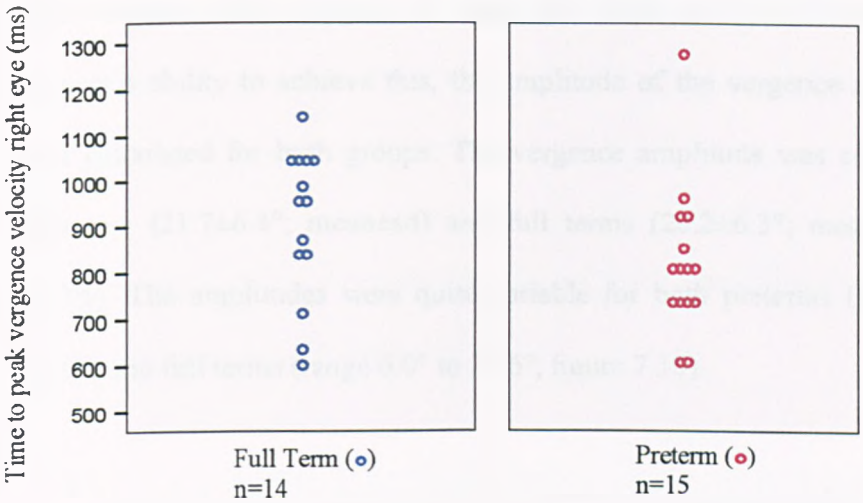


Figure 7.9 Distribution of the time to reach peak vergence velocity in the left eye (top) and right eye (bottom) in preterm (o) and full term (o) subjects

The differences between the left and right eye for peak vergence velocity and time to reach the peak velocity were assessed using the paired t-test (table 7.9). No statistically significant interocular differences were present for either measure in preterms or full terms.

Table 7.9 Difference between left eye and right eye for peak vergence velocity and time to peak velocity in preterms and full terms

Measurement of eye movement	Difference between left eye and right eye	
	Preterm mean±sd (significance)	Full Term mean±sd (significance)
Peak vergence velocity (deg/s)	5.7±61.2 (p=0.7)	38.1±86.8 (p=0.1)
Time to peak velocity (ms)	78.1±234.5 (p=0.2)	42.4±147.7 (p=0.3)

The vergence shift required to fixate the target was 25°. To determine the subject's ability to achieve this, the amplitude of the vergence angle executed was calculated for both groups. The vergence amplitude was similar for both preterms (21.7±6.4°; mean±sd) and full terms (20.2±6.3°; mean±sd, t= -0.6, p=0.5). The amplitudes were quite variable for both preterms (range 10.2° to 31.9°) and full terms (range 6.0° to 31.6°, figure 7.10).

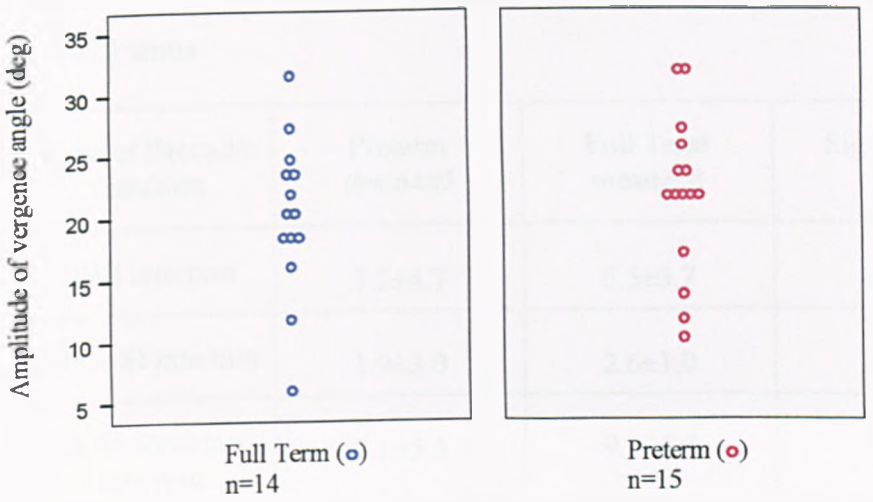


Figure 7.10 Distribution of the amplitude of the vergence angle in preterm (o) and full term (o) subjects

7.4 Control of fixation

In common with previous research, eye movement analysis was performed on one eye (Shaffer et al., 2003) as during binocular viewing the difference in fixation control between each eye is not significant (Abadi & Gowen, 2004). The distribution of square wave jerk (SWJ), 'other saccadic' intrusion (SI) and all

intrusions combined, rate, amplitude, peak velocity and duration, was assessed using the Kolmogorov-Smirnov test and found to be normal for both preterms and full terms (Appendix 2.8).

To assess the stability of fixation, the rate of SWJ, other SI and all SI combined per minute were measured (table 7.10).

Table 7.10 Comparison of the frequency of saccadic intrusions between preterms and full terms

Type of Saccadic intrusion	Preterm mean±sd	Full Term mean±sd	Significance
SWJ rate/min	7.2±4.7	6.5±3.7	p=0.7
Other SI rate/min	1.9±3.0	2.6±1.0	p=0.4
All SI combined rate/min	9.1±5.3	9.1±3.4	p=1.0

The rate per minute of all SI combined, SWJ and other SI was similar for both preterms and full terms with no statistically significant differences. The distribution of the rate of all combined SI's, SWJ's and other SI's is presented in Figure 7.11.

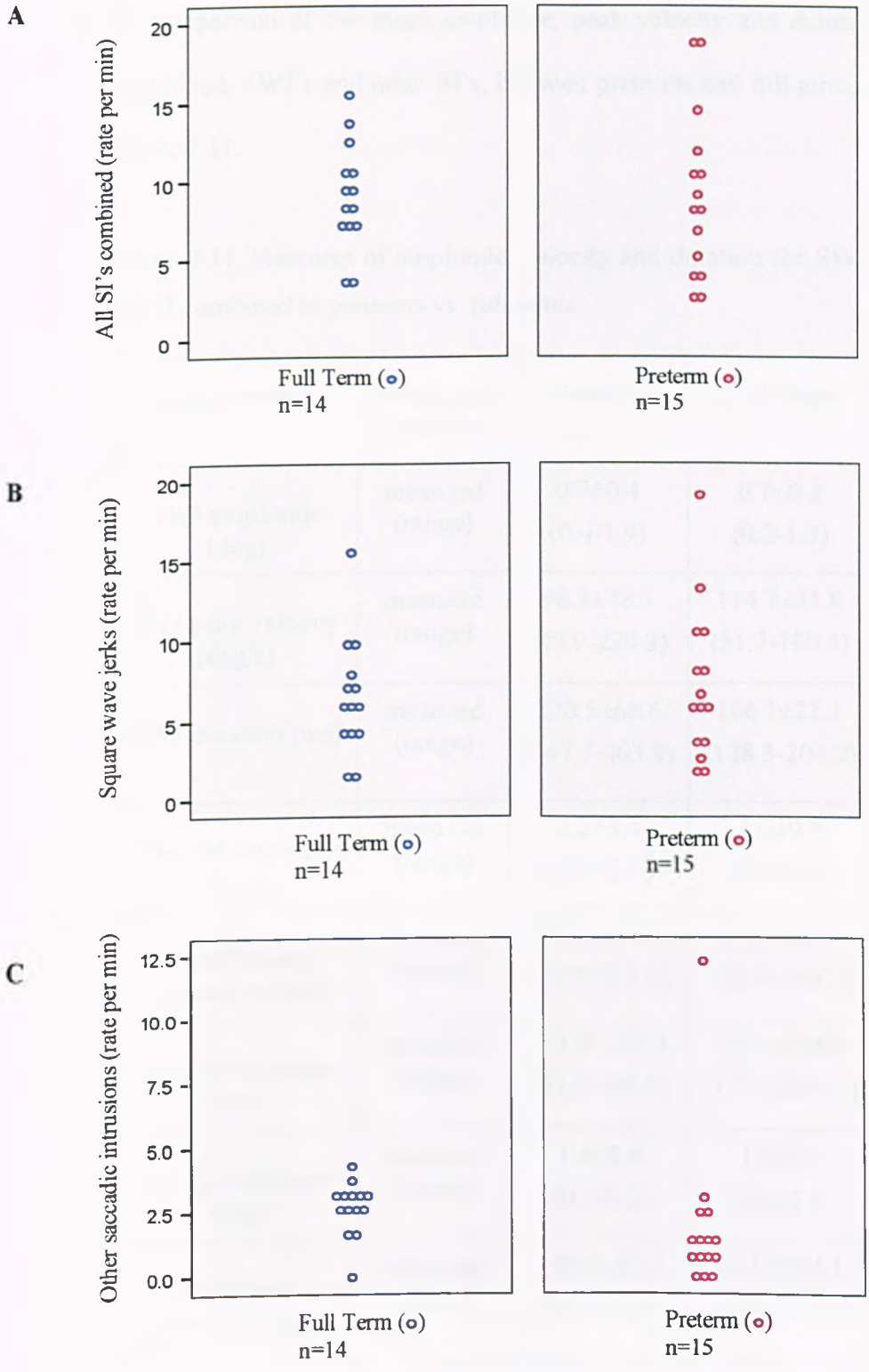


Figure 7.11 Distribution of the rate of all SI's combined (A), SWJ's (B) and other SI's (C) in preterm (o) and full term (o) subjects

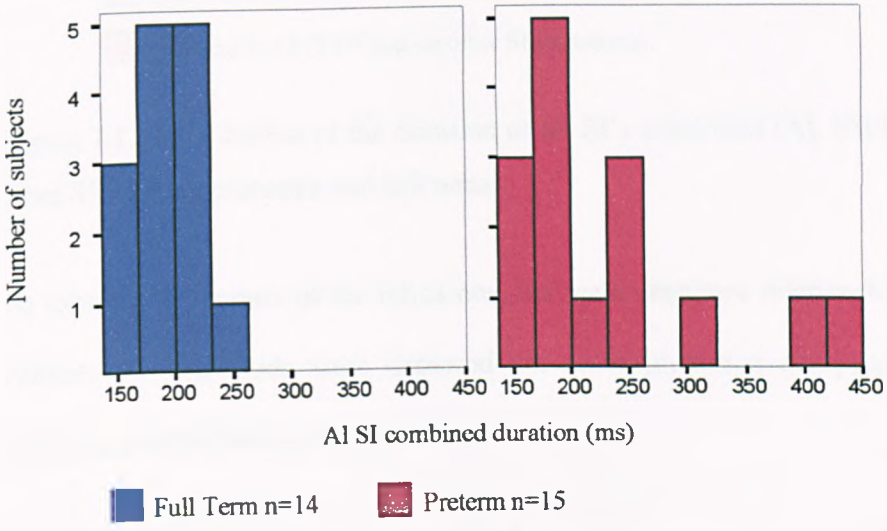
A comparison of the mean amplitude, peak velocity and duration for all SI's combined, SWJ's and other SI's, between preterms and full terms is provided in Table 7.11.

Table 7.11 Measures of amplitude, velocity and duration for SWJ, other SI and all SI combined in preterms vs. full terms

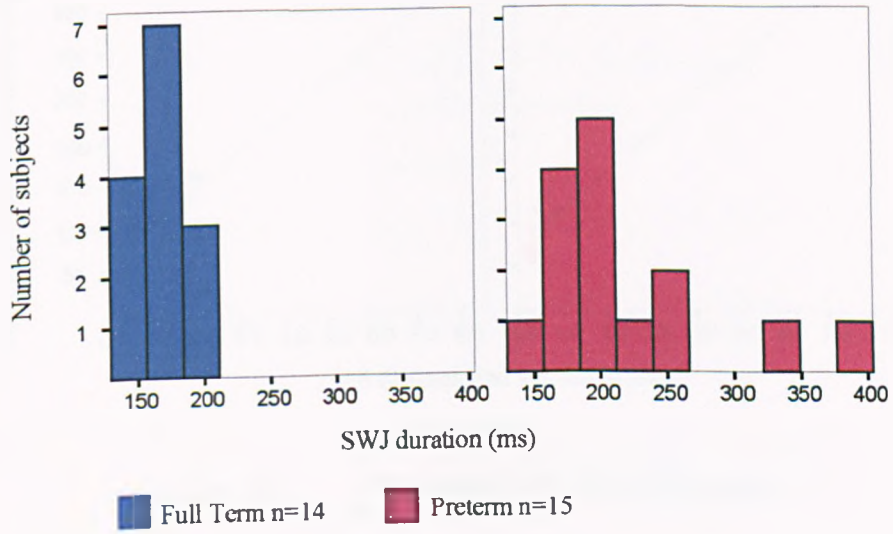
Measurement	Descriptive Statistics	Preterm	Full Term	Significance
SWJ amplitude (deg)	mean±sd (range)	0.7±0.4 (0.4-1.9)	0.7±0.3 (0.2-1.3)	p=0.8
SWJ peak velocity (deg/s)	mean±sd (range)	98.3±48.3 (49.9-229.3)	114.7±31.8 (51.7-180.3)	p=0.3
SWJ duration (ms)	mean±sd (range)	220.5±68.6 (147.5-403.8)	166.1±21.1 (128.3-204.2)	p=0.008
Other SI amplitude (deg)	mean±sd (range)	2.2±3.4 (0.1-12.0)	1.6±0.8 (0.6-3.2)	p=0.6
Other SI peak velocity (deg/s)	mean±sd (range)	159.0±140.0 (32.7-561.8)	111.6±28.4 (72.9-180.7)	p=0.2
Other SI duration (ms)	mean±sd (range)	271.8±159.4 (95.0-596.7)	225.4±54.8 (101.7-297.5)	p=0.3
All SI amplitude (deg)	mean±sd (range)	1.4±2.0 (0.3-8.2)	1.2±0.4 (0.6-2.1)	p=0.7
All SI peak velocity (deg/s)	mean±sd (range)	129.7±87.5 (60.5-399.8)	114.7±24.1 (58.8-160.0)	p=0.5
All SI duration (ms)	mean±sd (range)	231.1±85.8 (147.5-428.5)	191.3±25.6 (137.2-232.5)	p=0.1

Generally values were similar for preterms and full terms. The only significant difference was for the duration of SWJ's, which were longer for preterms. As with other measures of oculomotor control, the preterms showed greater variability for all fixation measures, with larger standard deviations. The extent of the variability for the duration of SWJ, other SI and all SI combined is illustrated in Figure 7.12.

A



B



C

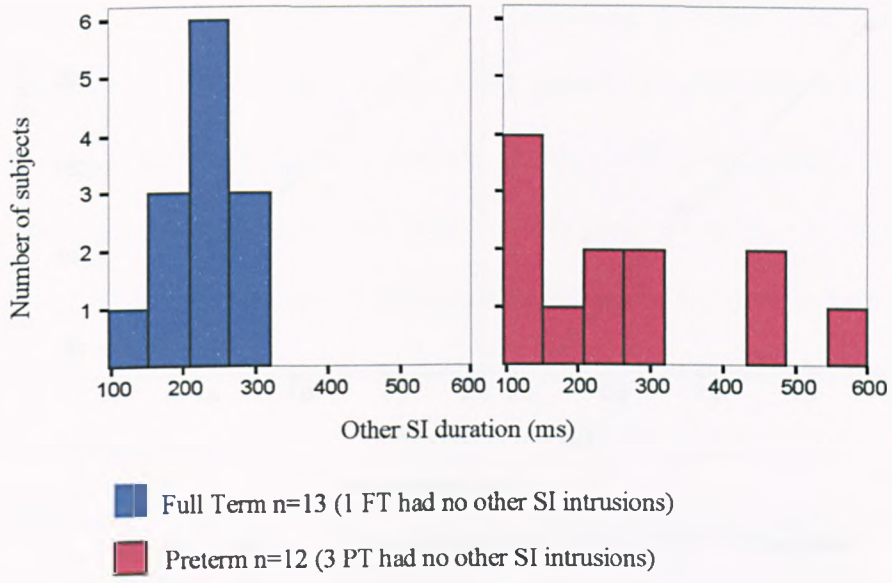
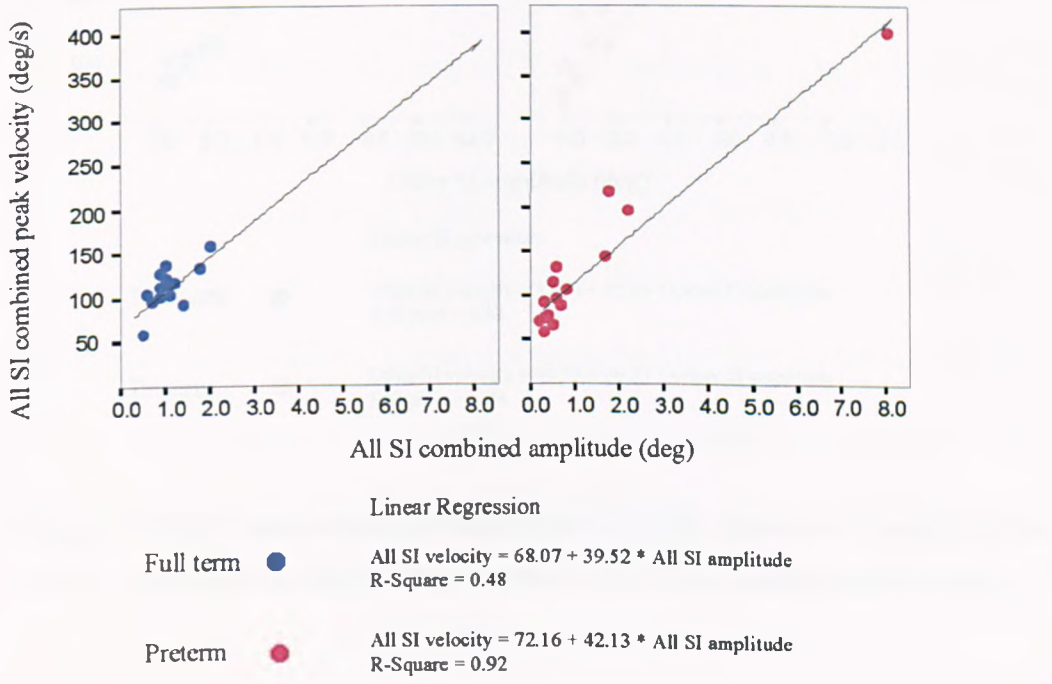


Figure 7.12 Distribution of the duration of all SI's combined (A), SWJ's (B) and other SI's (C) in preterms and full terms

To examine the nature of the intrusions, the main sequence relationships of peak velocity vs. amplitude were explored via scatterplots and compared between preterms and full terms (figures 7.13).

A



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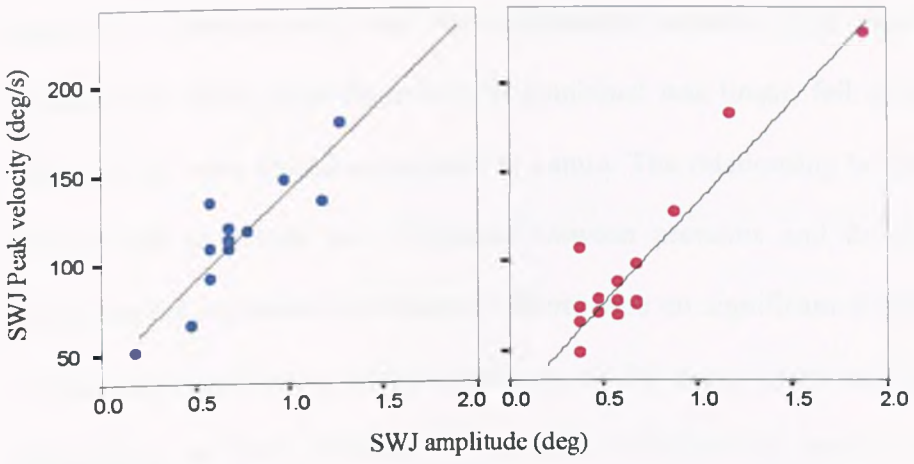
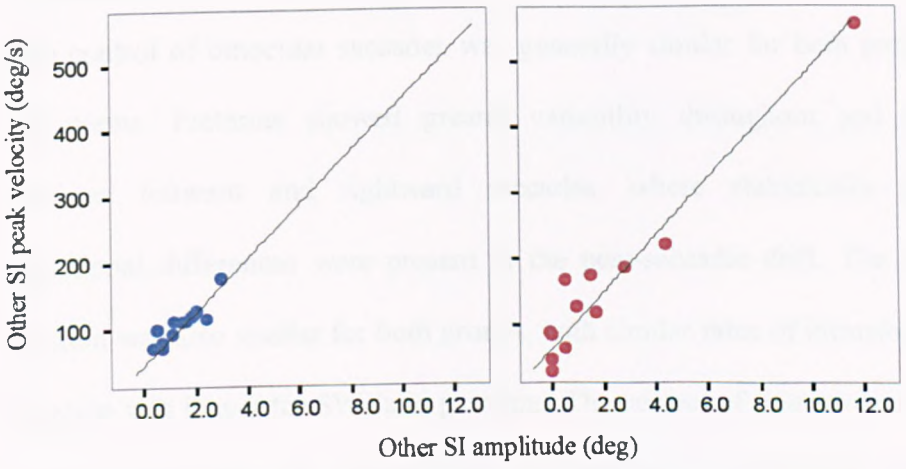


Linear Regression

Full term — Square wave jerk velocity = 40.41 + 101.03 * SWJ amplitude
R-Square = 0.78

Preterm — Square wave jerk velocity = 18.96 + 113.41 * SWJ amplitude
R-Square = 0.87

C



Linear Regression

Full term — Other SI velocity = 57.36 + 32.95 * Other SI amplitude
R-Square = 0.81

Preterm — Other SI velocity = 69.90 + 40.35 * Other SI amplitude
R-Square = 0.94

Figure 7.13 The main sequence relationships of peak velocity vs. amplitude for all SI's combined (A), SWJ's (B) and other SI's (C) in preterms and full terms

Figure 7.13 demonstrated that the relationship between peak velocity and amplitude for SWJ, other SI and all SI combined was linear, fell on the main sequence and were therefore saccadic in nature. The relationship between peak velocity and amplitude was compared between preterms and full terms by comparing the regression coefficients. There were no significant differences in the regression coefficients between preterms and full terms for the main sequence relationships in SWJ ($F=4.24$, $p>0.1$), other SI ($F=4.32$, $p>0.1$) or all SI combined ($F=4.24$, $p>0.1$), indicating that in each case the peak velocity-amplitude relationships were similar between preterms and full terms.

7.5 Summary and comparison with other data

The control of binocular saccades was generally similar for both preterms and full terms. Preterms showed greater variability throughout and especially between leftward and rightward saccades, where statistically significant directional differences were present in the post-saccadic drift. The control of fixation was also similar for both groups, with similar rates of intrusions, though duration was longer for SWJ's in preterms. The control of fixation and voluntary control of saccades are closely linked and both rely on inhibitory mechanisms (Munoz & Wurtz, 1992, Schlag-Rey et al., 1992). To determine if there was any association between the rate of saccadic intrusion and either the antisaccade error rate or proportion of express antisaccade errors (albeit with a small sample size), comparisons were made between the data and assessed using the Pearson Test (table 7.12 and 7.13). There were no statistically significant correlations between

the rate of saccadic intrusions and either the antisaccade directional error rate or proportion of express saccades.

Fixation measure	Correlation coefficient r and statistical significance	
	Preterm (n=15)	Full term (n=14)
Square wave jerk rate per minute	-0.01 (p=0.7)	0.01 (p=1.0)
Other SI rate per minute	0.4 (p=0.2)	0.3 (p=0.3)
All SI rate per minute	0.1 (p=0.7)	0.1 (p=0.7)

Table 7.12 Correlation between the rate of saccadic intrusions and the antisaccade directional error rate in preterms and full terms

Fixation measure	Correlation coefficient r and statistical significance	
	Preterm (n=15)	Full term (n=14)
Square wave jerk rate per minute	0.4 (p=0.2)	-0.2 (p=0.6)
Other SI rate per minute	-0.1 (p=0.7)	0.2 (p=0.5)
All SI rate per minute	0.3 (p=0.3)	-0.1 (p=0.7)

Table 7.13 Correlation between the rate of saccadic intrusions and the proportion of express antisaccade errors in preterms and full terms

An important difference was revealed between preterms and full terms when vergence was assessed. Preterms had significantly longer latencies and greater

variability between the left eye and right eye than full terms. To determine if vergence latency was associated with the degree of prematurity, scatterplots with linear regression were generated and Pearson's test used to assess the presence of any correlation (figure 7.14). There was negative correlation between vergence latency and GA which was stronger for the left eye than the right eye, but neither correlation was statistically significant.

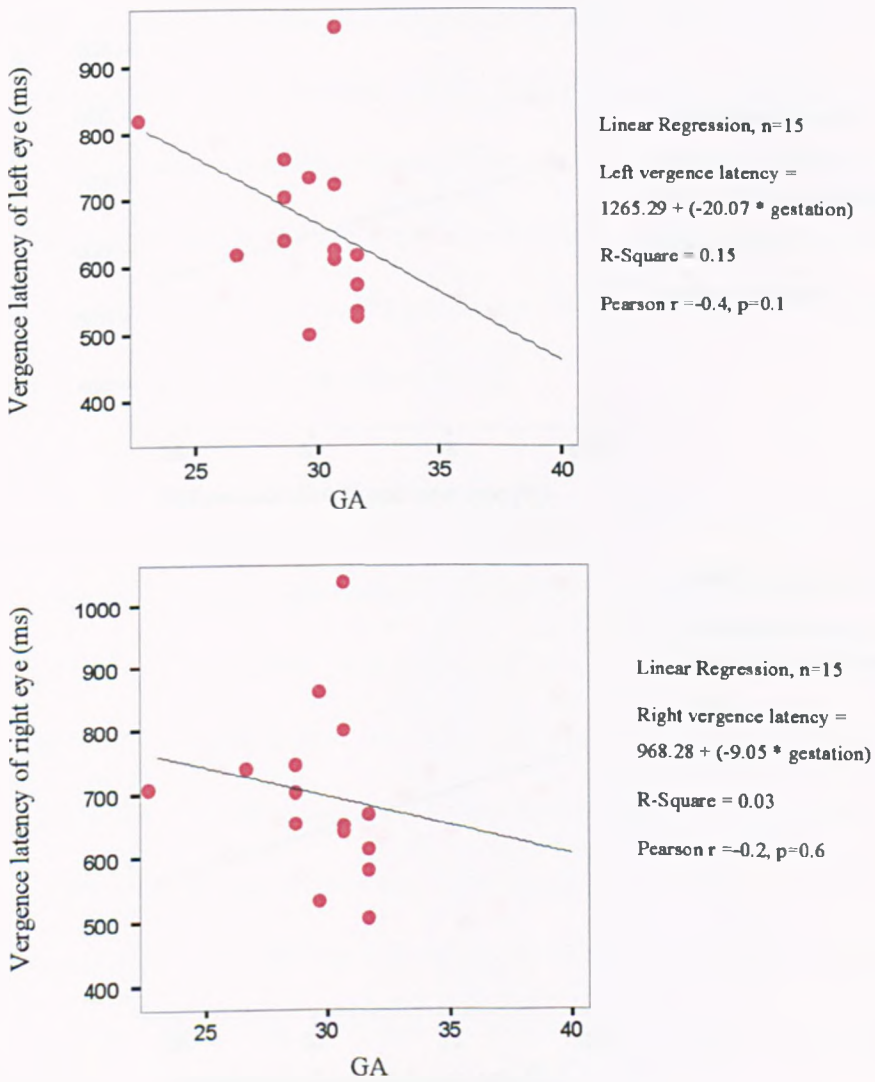


Figure 7.14 Correlation between vergence latency (left eye: top, right eye: bottom) and GA in preterms

The main deficits in preterms were found in the areas of antisaccades and vergence, with increased directional error rates and longer vergence latencies in comparison to full term controls. Scatterplots and Pearson's test were used to determine if these deficits were associated (figure 7.15). Vergence latency (left eye and right eye) showed a tendency to be positively correlated with antisaccade directional error rate, but did not reach statistical significance.

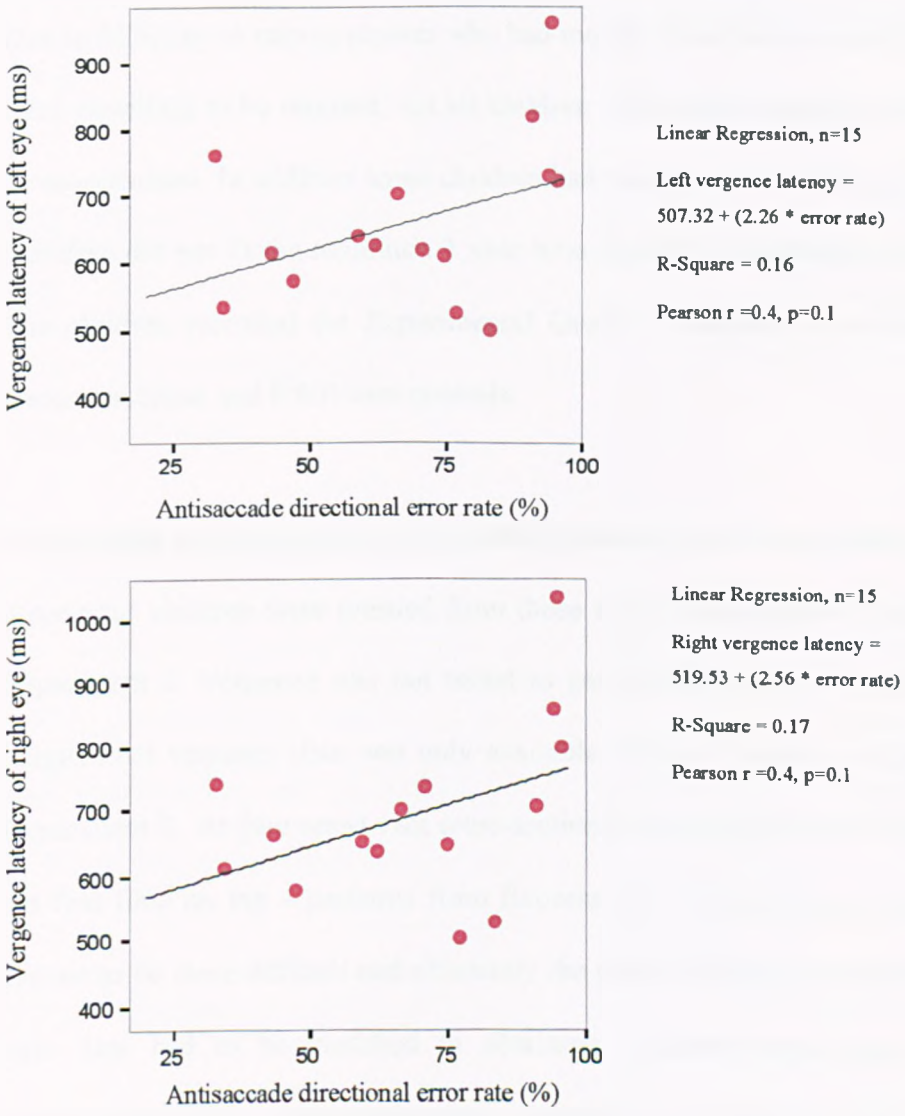


Figure 7.15 Correlation between vergence latency (left eye: top, right eye: bottom) and antisaccade directional error rate in preterms

CHAPTER 8: Development of antisaccade and vergence control in children born preterm vs. full term (Experiments 3a and 3b)

8.1 Experiment 3a (assessment at 13-14 years)

To examine the effect of development on the main areas of oculomotor deficit found in preterms, repeat measurements of antisaccades and vergence were collected on preterms and full terms at 3-5 years after they were initially tested. Due to difficulty in tracing parents who had moved out of the area and those who were unwilling to be retested, not all children who were originally tested could be re-examined. In addition some children had been seen relatively recently and therefore did not fit the minimum 3 year time period for longitudinal follow up. The children recruited for Experimental Group 3 therefore comprised of 10 preterm subjects and 8 full term controls.

Longitudinal antisaccade data was available however for all ten preterm subjects, 4 preterms children were retested from those seen in Experiment 1 and 6 from Experiment 2. Vergence was not tested as part of Experiment 1 and therefore longitudinal vergence data was only available for the 6 preterm children from Experiment 2. At their retest visit cross-sectional vergence data was collected for the first time on the 4 preterms from Experiment 1. Recruitment of full terms proved to be more difficult and ultimately the goal of obtaining longitudinal full term data had to be modified to obtaining a cross-sectional age matched comparison group. Antisaccades were retested on 3 full term children from Experiment 1 and their vergence was assessed for the first time. It was not

possible to recruit any full terms from those who were tested in Experiment 2. In order to increase the number of full term subjects, an additional 5 full terms that had not been previously tested, but were a similar age to the other children in both preterm and full term cohorts, were recruited. Both antisaccade and vergence data was collected on the extra 5 full term children. A combination of longitudinal, but mainly cross-sectional antisaccade data was therefore available for 8 full term children and cross-sectional vergence data also available for 8 full terms.

Both preterm and full term groups again coped well with the testing, with no notable differences. Testing time was slightly less for this experiment, as only antisaccades and vergence were tested, ranging between 30-40 minutes including time for rest breaks.

8.1i Statistical analysis

The number of subjects in both preterm and full term groups was relatively low, making it unfeasible to determine if the data was normally distributed. All data, both demographic and oculomotor, was therefore analysed using a non-parametric test for unpaired subjects, the Mann-Whitney U Test.

The demographics of both groups are presented in Table 8.1. Preterms and full terms were compared for their age when tested and their IQ. There were no

significant differences between the groups for either their age (U=24.5, p=0.2) or IQ (U=34.0, p=0.6).

Table 8.1 Demographics of preterm and full term children recruited for Experiment 3a

Descriptive statistics		PT	FT
Number of subjects (longitudinal+cross-sectional)	Antisaccade	10 (10+0)	8 (3+5)
	Vergence	10 (6+4)	8 (0+8)
Median age when tested in months and (IQR)		163.5 (161.0, 170.8)	168.0 (162.8, 177.0)
Median full scale IQ and (IQR)		97 (94, 103)	101 (93, 106)
Median GA (weeks) and (IQR)		29.5 (27.0, 31.3)	37+
Median birth weight in grams and (IQR)		1336 (1144, 1703	N/A

To determine if the preterm children that were followed up were representative of the main preterm group, the antisaccade (table 8.2) and vergence (table 8.3) baseline measurements (at their first assessment) of the preterm follow ups and the remainder of the main preterm group were compared using the Mann-Whitney U Test. No statistically significant differences were present for antisaccades or vergence, though the proportion of express saccades and peak vergence velocities were slightly lower for the follow up group.

Table 8.2 Comparison of antisaccade measures between the preterm follow ups and the remaining main preterm group

Measurement	Descriptive statistics	Preterm follow-ups, n=10	Main preterm group, n=25	Mann-Whitney U
Antisaccade directional error rate (%)	Median (IQR)	72.3 (62.5, 81.7)	74.2 (58.7, 91.6)	p=0.8
Antisaccade rejection rate (%)	Median (IQR)	7.8 (5.6, 13.8)	7.3 (3.1, 11.0)	p=0.3
Latency of antisaccade error (ms)	Median (IQR)	197.0 (184.9, 224.5)	199.3 (175.0, 213.6)	p=0.3
Proportion of express antisaccade errors (%)	Median (IQR)	6.3 (3.1, 20.9)	16.7 (6.8, 29.7)	p=0.2
Antisaccade error correction rate (%)	Median (IQR)	90.2 (86.6, 92.1)	93.5 (82.3, 96.6)	p=0.7
Latency of antisaccade (ms)	Median (IQR)	384.2 (350.2, 408.2)	348.9 (294.6, 388.8)	p=0.1

Table 8.3 Comparison of vergence measures between the preterm follow ups and the remaining main preterm group

Measurement	Descriptive statistics	Preterm follow-ups, n=6	Main preterm group, n=9	Mann-Whitney
Vergence latency, left eye (ms)	Median (IQR)	634.6 (591.1, 733.5)	621.3 (555.8, 748.7)	p=1.0
Vergence latency, right eye (ms)	Median (IQR)	654.3 (607.9, 706.2)	742.0 (598.4, 832.7)	p=0.3
Vergence peak velocity, left eye (deg/s)	Median (IQR)	161.3 (118.2, 216.2)	216.7 (176.1, 261.1)	p=0.07
Vergence peak velocity, right eye (deg/s)	Median (IQR)	-176.8 (-99.2, -264.4)	-211.5 (-170.1, -270.7)	p=0.4
Time to reach peak velocity, left eye (ms)	Median (IQR)	921.5 (773.0, 1133.2)	925.5 (688.3, 1054.3)	p=0.9
Time to reach peak velocity, right eye (ms)	Median (IQR)	749.4 (725.9, 1015.8)	823.3 (710.5, 892.0)	p=0.8
Vergence angle (deg)	Median (IQR)	22.1 (20.1, 24.3)	22.0 (12.7, 29.4)	p=1.0

8.1ii Antisaccade data in Experiment 3a (age 13-14 years)

To determine if antisaccade control had improved in both preterms and full terms, comparison of the antisaccade measurements was made between the first and final assessment of preterms (First assessment: 124, IQR 109,128; Final assessment: 164, IQR 161,171; median and IQR age in months) and full terms (First assessment: 103, IQR 103,114; Final assessment: 162, IQR 162,166; median and IQR age in months). The Wilcoxon Test was used (paired test for non-parametric data) to check for significant differences as the measurements were performed on the same subjects longitudinally (table 8.4).

Large reductions in the antisaccade directional error rate had occurred (figure 8.1) during the time between assessments (PT: 40 months, FT: 59 months; median), especially for the preterms. Notable reductions also occurred for preterms in the latency of the antisaccade and latency of the antisaccade error and improvements were also made in the antisaccade error correction rate.

Table 8.4 Comparison of longitudinal antisaccade data in preterms and full terms using the Wilcoxon Test

Measure	Descriptive Statistics	Preterms (n=10)			Full Terms (n=3)		
		First Assess	Final Assess	Sig. p value	First Assess	Final Assess	Sig. p value
Antisaccade directional error rate (%)	Median	72.3	35.5	p=0.005	59.8	37.8	p=0.1
		Difference -36.8			Difference -22.0		
	IQR	(62.5, 81.7)	(29.3, 52.7)		(48.0, 60.4)	(30.2, 39.5)	
Latency of antisaccade error (ms)	Median	196.6	182.5	p=0.09	193.2	196.7	p=0.3
		Difference -14.1			Difference +3.5		
	IQR	(184.9, 224.5)	(165.7, 210.7)		(174.2, 219.4)	(161.1, 207.8)	
Proportion of express antisaccade errors (%)	Median	6.3	10.4	p=0.6	2.9	5.0	p=0.2
		Difference +4.1			Difference +2.1		
	IQR	(3.1, 20.9)	(0, 28.4)		(0, 17.1)	(0, 22.5)	
Antisaccade error correction rate (%)	Median	90.2	100.0	p=0.01	100.0	100.0	p=0.3
		Difference +9.8			Difference 0.0		
	IQR	(86.6, 92.1)	(100.0, 100.0)		(76.5, 100.0)	(98.2, 100.0)	
Latency of antisaccade (ms)	Median	384.2	328.3	p=0.02	439.4	344.4	p=0.3
		Difference -55.9			Difference -95.0		
	IQR	(350.2, 408.2)	(277.8, 355.9)		(333.7, 439.7)	(282.6, 385.2)	

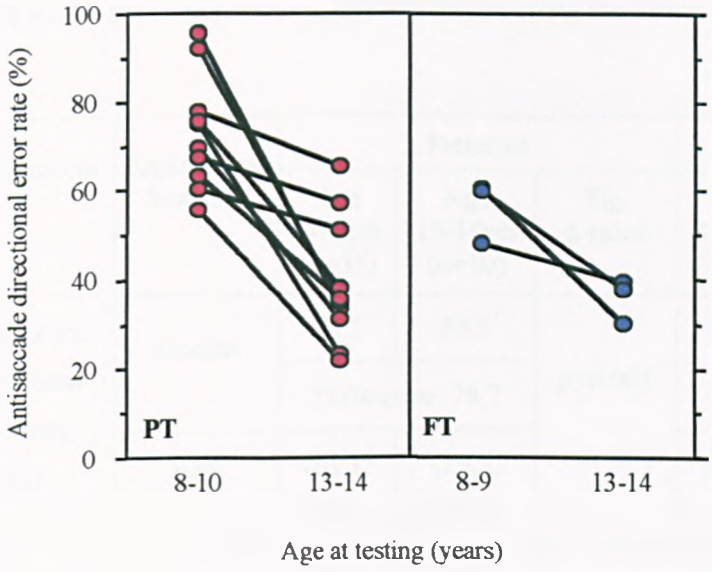


Figure 8.1 Antisaccade directional error rates in preterms (n=10) and full terms (n=3), showing differences between the first assessment at age 8-10 years and the final assessment at age 13-14 years.

As the sample size was particularly low for the longitudinal full term group and could be at risk from a Type II error (null hypothesis fails to be rejected when it is false because of a small sample size), additional analysis was performed to assess the improvement in control as the children got older. A comparison was made using a combination of longitudinal and cross-sectional data for both preterms and full terms, between the age groups of 8-11 years (Groups 1 and 2) and 13-14 years (Group 3). The full term group at age 13-14 years still had a sample size of less than ten and therefore a non-parametric test, the Mann-Whitney U Test was used (Table 8.5).

Table 8.5 Comparison of antisaccade data between the age groups of 8-11 years and 13-14 years in preterms and full terms using the Mann-Whitney U Test

Measurement	Descriptive Statistics	Preterms			Full Terms		
		Age 8-11yrs (n=35)	Age 13-14yrs (n=10)	Sig. p value	Age 8-11yrs (n=32)	Age 13-14yrs (n=8)	Sig. p value
Antisaccade directional error rate (%)	Median	74.2	35.5	p<0.001	57.0	39.2	p=0.01
		Difference -38.7			Difference -17.8		
	IQR	(61.1, 87.9)	(29.3, 52.7)		(39.5, 64.7)	(32.1, 45.1)	
Latency of antisaccade error (ms)	Median	199.3	182.5	p=0.3	209.0	189.0	p=0.1
		Difference -16.8			Difference -20.0		
	IQR	(179.0, 216.4)	(165.7, 210.7)		(186.1, 240.6)	(165.0, 208.4)	
Proportion of express antisaccade errors (%)	Median	13.6	10.4	p=0.7	8.2	4.5	p=0.5
		Difference -3.2			Difference -3.7		
	IQR	(5.0, 25.0)	(0, 28.4)		(0, 16.9)	(0.8, 12.9)	
Antisaccade error correction rate (%)	Median	90.3	100.0	p=<0.001	97.7	100.0	p=0.02
		Difference +9.7			Difference +2.3		
	IQR	(83.3, 95.8)	(100.0, 100.0)		(86.5, 100.0)	(100.0, 100.0)	
Latency of antisaccade (ms)	Median	353.0	328.3	p=0.06	346.0	357.9	p=0.8
		Difference -24.7			Difference +11.9		
	IQR	(325.8, 395.8)	(277.8, 355.9)		(300.7, 371.3)	(288.5, 387.4)	

Between the age groups of 8-11 and 13-14 years the difference between the cross-sectional data revealed that the antisaccade directional error rate had significantly reduced for both preterms and full terms. Additionally, both groups showed a small, but significant increase in the antisaccade error correction rate and preterms showed a reduction in the latency of the antisaccade, which approached significance. Whilst both preterms and full terms made improvements in the control of antisaccades, to assess if the two groups still showed differences on the antisaccade measures, comparisons were made using the Mann-Whitney U Test, with the additional 5 full term controls aged 13-14 years (table 8.6).

Table 8.6 Comparison of antisaccade control at the final assessment, age 13-14 years, in preterms vs. full terms

Measurement	Descriptive statistics	Preterm follow-ups, n=10	Full terms, n=8	Mann-Whitney
Antisaccade directional error rate (%)	Median (IQR)	35.5 (29.3, 52.7)	39.2 (32.1, 45.1)	p=0.7
Antisaccade rejection rate (%)	Median (IQR)	2.1 (1.0, 5.2)	0.5 (0.0, 4.5)	p=0.2
Latency of antisaccade error ms)	Median (IQR)	182.5 (165.7, 210.7)	189.0 (165.0, 208.4)	p=1.0
Proportion of express antisaccade errors (%)	Median (IQR)	10.4 (0, 28.4)	4.5 (0.8, 12.9)	p=0.3
Antisaccade error correction rate (%)	Median (IQR)	100.0 (100.0, 100.0)	100.0 (100.0, 100.0)	p=1.0
Latency of antisaccade (ms)	Median (IQR)	328.3 (277.8, 355.9)	357.9 (288.5, 387.4)	p=0.5

By the age of 13-14 years there was no longer any significant difference in the antisaccade directional error rate between preterms and full terms. The latency of the antisaccade error, proportion of express antisaccade errors and rate at which the antisaccade errors were corrected, were also now similar for both groups. The distribution of the directional error rate, proportion of express antisaccade errors and latency of the antisaccade error are illustrated in Figures 8.2, 8.3 and 8.4.

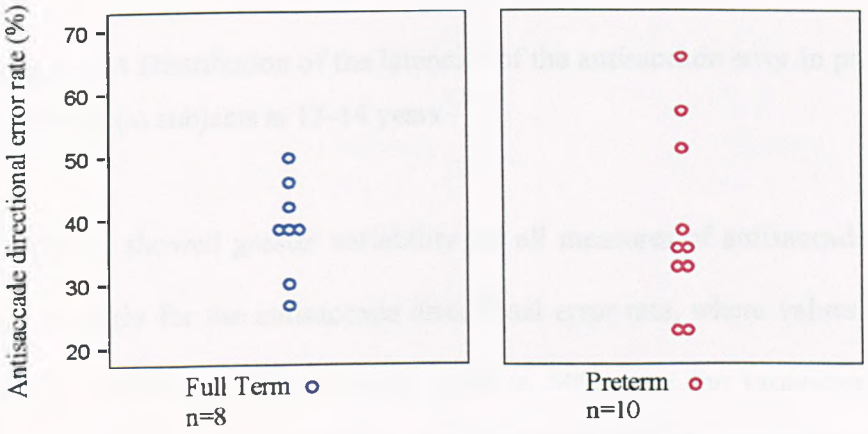


Figure 8.2 Distribution of the antisaccade error rate in preterm (o) and full term (o) subjects at 13-14 years

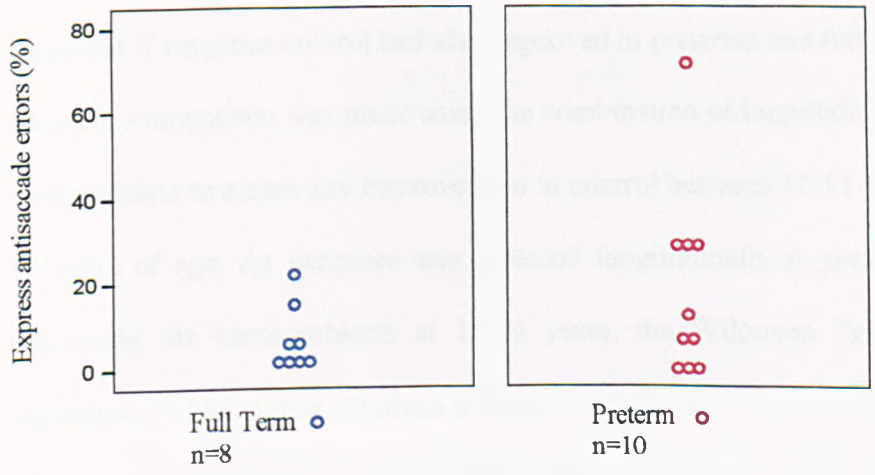


Figure 8.3 Distribution of express antisaccade errors in preterm (o) and full term (o) subjects at 13-14 years

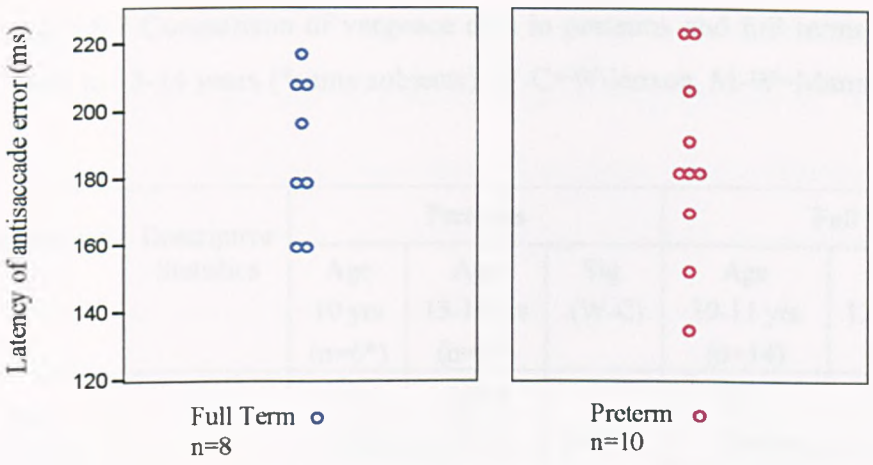


Figure 8.4 Distribution of the latencies of the antisaccade error in preterm (o) and full term (o) subjects at 13-14 years

Preterms showed greater variability for all measures of antisaccade control and particularly for the antisaccade directional error rate, where values ranged from 22% to 66% (compared to FT, 27% to 50%) and the proportion of express antisaccade errors, which ranged from 0% to 71% (compared to FT, 0% to 23%).

8.1iii Vergence data in Experiment 3a (age 13-14 years)

To assess if vergence control had also improved in preterms and full terms by 13-14 years, comparison was made using the combination of longitudinal and cross-sectional data to assess any improvement in control between 10-11 years and 13-14 years of age. As vergence was assessed longitudinally in preterms, by re-examining the same subjects at 13-14 years, the Wilcoxon Test was used. Assessment of full terms involved different subjects at 13-14 years and therefore analysis was undertaken using the Mann-Whitney U Test. A summary of the data is provided in Table 8.7.

Table 8.7 Comparison of vergence data in preterms and full terms, from 10-11 years to 13-14 years (*same subjects), W-C=Wilcoxon, M-W=Mann-Whitney U

Measurement	Descriptive Statistics	Preterms			Full Terms		
		Age 10 yrs (n=6*)	Age 13-14 yrs (n=6*)	Sig. (W-C)	Age 10-11 yrs (n=14)	Age 13-14 yrs (n=8)	Sig. (M-W)
Left vergence latency (ms)	Median	634.6	567.8	p=0.08	552.2	493.8	p=0.2
		Difference -66.8			Difference -58.4		
	IQR	(591.1, 733.5)	(506.5, 646.5)		(480.1, 595.9)	(460.9, 533.3)	
Right vergence latency (ms)	Median	654.3	578.9	p=0.3	530.4	477.7	p=0.2
		Difference -75.4			Difference -52.7		
	IQR	(607.9, 706.2)	(534.4, 663.1)		(431.4, 591.5)	(394.8, 533.2)	
Left vergence peak velocity (deg/s)	Median	161.3	152.8	p=0.5	218.1	181.8	p=0.2
		Difference -8.5			Difference -36.3		
	IQR	(118.2, 216.2)	(85.9, 322.1)		(155.1, 265.7)	(80.5, 221.1)	
Right vergence peak velocity (deg/s)	Median	-176.8	-151.7	p=0.2	-180.0	-173.2	p=0.8
		Difference -25.1			Difference -6.8		
	IQR	(-99.2, -176.8)	(-95.0, -193.9)		(-137.7 -210.6)	(-134.3 -228.6)	
Left time to peak velocity (ms)	Median	921.5	816.7	p=0.2	848.9	735.5	p=0.1
		Difference -104.8			Difference -113.4		
	IQR	(773.0, 1133.2)	(672.5, 1002.7)		(780.7, 970.2)	(609.6, 820.1)	
Right time to peak velocity (ms)	Median	749.4	778.6	p=0.6	959.7	615.4	p=0.01
		Difference +29.2			Difference -344.3		
	IQR	(725.9, 1015.8)	(738.3, 974.9)		(799.7, 1048.3)	(544.1, 776.8)	
Amplitude of vergence angle (deg)	Median	22.1	20.2	p=0.9	20.4	20.9	p=0.8
		Difference -1.9			Difference +0.5		
	IQR	(20.1, 24.3)	(12.6, 26.0)		(17.7, 24.1)	(15.4, 30.5)	

There were notable reductions in vergence latency for both preterms and full terms, though statistical significance was only approached for the left eye in preterms. Also the time to reach the peak vergence velocity reduced in full terms and in the left eye only for preterms. The peak velocities also reduced slightly for both groups, but again were not statistically significant.

At age 10-11 years the vergence latency was significantly longer in preterms than full terms. At 13-14 years both groups have shown reductions in their latencies. To assess if the initiation of vergence was still slower in preterms at 13-14 years both groups were compared for this and all other vergence measures using the Mann-Whitney U Test (table 8.8).

Table 8.8 Comparison of vergence control at 13-14 years in preterms vs. full terms

Measurement	Descriptive statistics	Preterms age 13-14 yrs n=10	Full terms age 13-14 yrs n=8	Sig. (M-W)
Left vergence latency (ms)	Median (IQR)	563.8 (493.7, 619.5)	493.8 (460.9, 533.3)	p=0.03
Right vergence latency (ms)	Median (IQR)	540.0 (496.1, 623.1)	477.7 (394.8, 533.2)	p=0.02
Left vergence peak velocity (deg/s)	Median (IQR)	111.0 (87.2, 218.5)	181.8 (80.5, 221.1)	p=0.8
Right vergence peak velocity (deg/s)	Median (IQR)	-132.7 (-108.7, -181.8)	-173.2 (-134.3, -228.6)	p=0.2
Left time to peak velocity (ms)	Median (IQR)	816.7 (625.3, 944.5)	735.5 (609.6, 820.1)	p=0.5
Right time to peak velocity (ms)	Median (IQR)	760.4 (639.5, 853.6)	615.4 (544.1, 776.8)	p=0.2
Amplitude of vergence angle deg)	Median (IQR)	19.1 (14.7, 25.0)	20.9 (15.4, 30.5)	p=0.6

At the age of 13-14 years although vergence latencies had reduced in both preterms and full terms, the latencies were still significantly longer for the preterm group. Additionally, preterms had lower peak vergence velocities and took longer to reach the peak velocity, though neither difference was statistically significant. The distribution of the vergence latencies and peak velocities are illustrated in Figures 8.5 and 8.6.

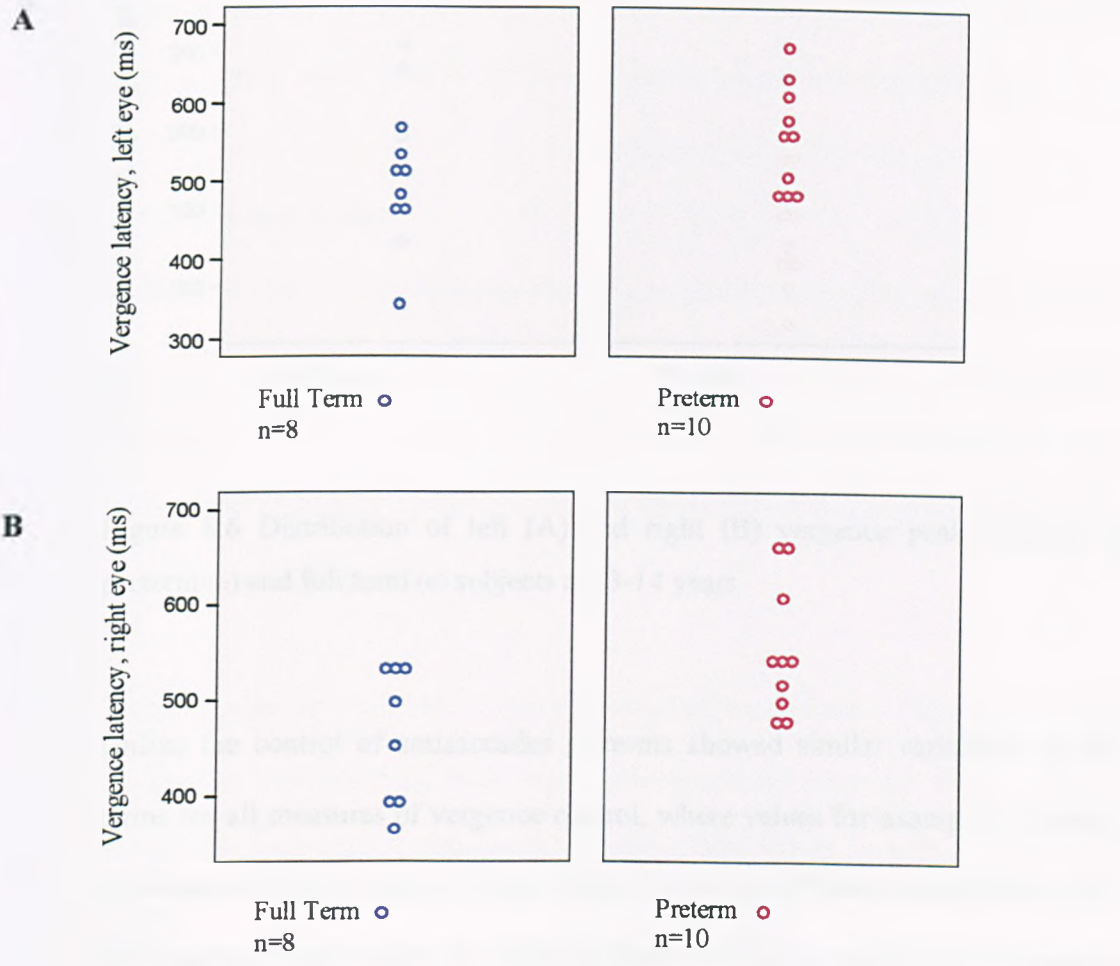
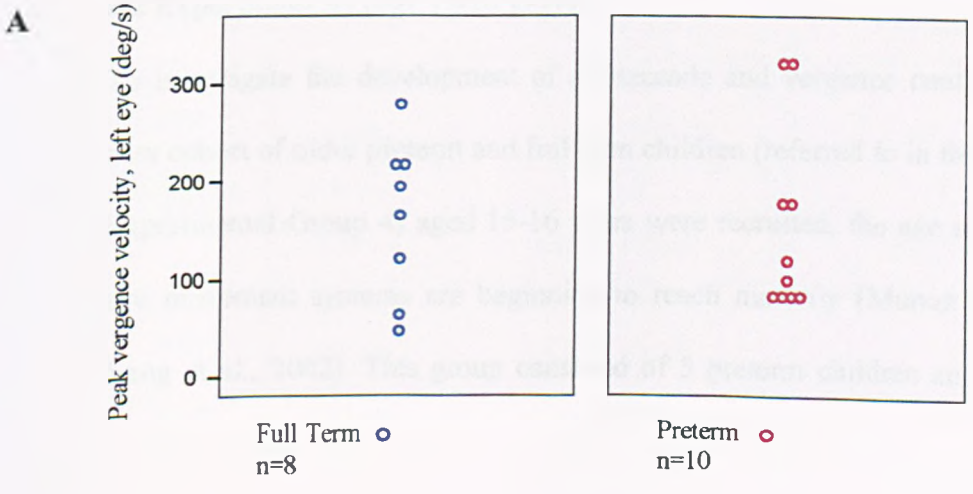


Figure 8.5 Distribution of left (A) and right (B) vergence latencies in preterm (o) and full term (o) subjects at 13-14 years



B

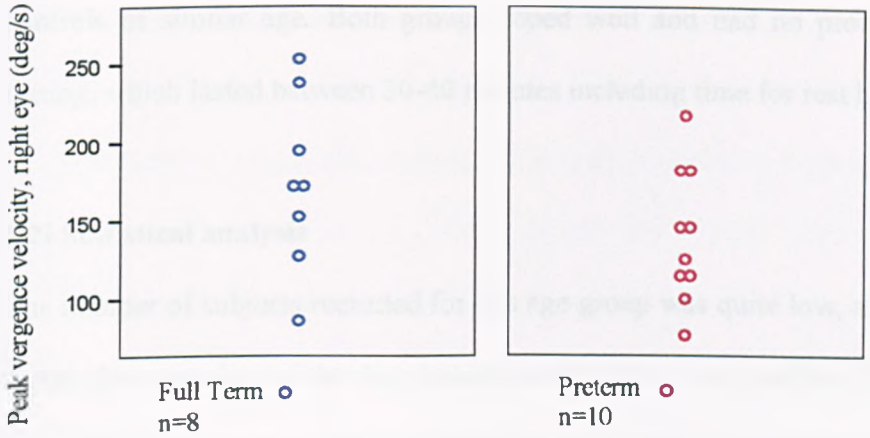


Figure 8.6 Distribution of left (A) and right (B) vergence peak velocity in preterm (o) and full term (o) subjects at 13-14 years

Unlike the control of antisaccades preterms showed similar variability to full terms for all measures of vergence control, where values for example of latency in preterms ranged in the left eye from 477.9ms to 675.6ms (compared to FT, 347.0ms to 571ms) and in the right eye from 476.7ms to 666.3ms (compared to FT, 366.7ms to 536.9ms).

8.2 Experiment 3b (age 15-16 years)

To investigate the development of antisaccade and vergence control further, a new cohort of older preterm and full term children (referred to in the Methods as Experimental Group 4) aged 15-16 years were recruited, the age at which both eye movement systems are beginning to reach maturity (Munoz et al., 1998, Yang et al., 2002). This group consisted of 5 preterm children and 5 full term

controls of similar age. Both groups coped well and had no problems during testing, which lasted between 30-40 minutes including time for rest breaks.

8.2i Statistical analysis

The number of subjects recruited for this age group was quite low, and to try and assess the normality of the distribution was therefore not possible. All data both demographic and oculomotor was therefore analysed by non-parametric methods, using either the Mann-Whitney U Test or Kruskal-Wallis Test (where more than 2 groups were compared).

The demographics of both groups are presented in Table 8.9. Preterms and full terms were compared for their age when tested and their IQ. There were no statistically significant differences for either age (U=9, p=0.5) or IQ (U=7, p=0.3).

Table 8.9 Demographics of preterm and full term children recruited for Experiment 3b.

Descriptive Statistics		Preterm (n=5)	Full Term (n=5)
Age when tested in months	Median	196.0	190.0
	(IQR)	(193.5, 197.0)	(180.5, 199.0)
Full Scale IQ	Median	94.0	103.0
	(IQR)	(86.5, 102.0)	(90.5, 109.5)
GA in weeks	Median	31.0	37+
	(IQR)	(28.5, 31.0)	37+
Birth weight in grams	Median	1268	N/A
	(IQR)	(1013, 1462)	N/A

8.2ii Antisaccade data in Experiment 3b (age 15-16 years)

To determine if the control of antisaccades had improved with age in preterms and full terms, a comparison of antisaccade measurements was made between all 3 age groups tested (8-11 yrs, 13-14 yrs and 15-16 yrs). A summary of the antisaccade measurements for the 3 age groups and statistical significance (using the Kruskal-Wallis test) of any difference is provided in Tables 8.10 (PT) and 8.11 (FT).

Table 8.10 Comparison of antisaccade measures at ages 8-11, 13-14 and 15-16 years in preterms (Kruskal-Wallis)

Measure	Descriptive Statistic	Age 8-11 years	Age 13-14 years	Age 15-16 years	Sig.
Antisaccade directional error rate (%)	Median	74.2	35.5	23.7	p=0.001
	(IQR)	(61.1, 87.9)	(29.3, 52.7)	(15.1, 33.4)	
	Range	33.7-100.0	22.0-65.6	13.5-37.5	
Latency of antisaccade error (ms)	Median	199.3	182.5	186.7	p=0.6
	(IQR)	(179.0, 216.4)	(165.7, 210.7)	(161.4, 242.2)	
	Range	140.9-255.4	135.0-224.0	160.1-257.4	
Prop. of express antisaccade errors (%)	Median	13.6	10.4	10.5	p=0.8
	(IQR)	(5.0, 25.0)	(0.0, 28.4)	(4.6, 19.6)	
	Range	0.0-80.0	0.0-71.4	0.0-25.5	
Antisaccade error correction rate (%)	Median	90.3	100.0	100.0	p=0.001
	(IQR)	(83.3, 95.8)	(100.0, 100.0)	(100.0, 100.0)	
	Range	66.6-100.0	84.3-100.0	100.0-100.0	
Latency of antisaccade (ms)	Median	353.0	328.3	284.6	p=0.008
	(IQR)	(325.8, 395.8)	(277.8, 355.9)	(278.1, 311.3)	
	Range	223.3-474.6	252.1-401.6	278.0-336.9	

Table 8.11 Comparison of antisaccade measures at ages 8-11, 13-14 and 15-16 years in full terms (Kruskal-Wallis)

Measure	Descriptive Statistic	Age 8-11 years	Age 13-14 years	Age 15-16 years	Sig.
Antisaccade directional error rate (%)	Median	57.0	39.2	13.8	p=0.001
	(IQR)	(39.5, 64.7)	(32.1, 45.1)	(11.3, 25.6)	
	Range	20.0-91.8	26.8-50.0	10.8-32.3	
Latency of antisaccade error (ms)	Median	209.0	189.0	207.6	p=0.2
	(IQR)	(186.1, 240.6)	(165.0, 208.4)	(201.3, 231.0)	
	Range	149.8-298.1	158.2-217.2	197.1-245.5	
Prop. of express antisaccade errors (%)	Median	8.2	4.5	0.0	p=0.1
	(IQR)	(0.0, 16.9)	(0.8, 12.9)	(0.0, 3.9)	
	Range	0.0-51.8	0.0-22.5	0.0-7.7	
Antisaccade error correction rate (%)	Median	97.7	100.0	100.0	p=0.01
	(IQR)	(86.5, 100.0)	(100.0, 100.0)	(100.0, 100.0)	
	Range	72.4-100.0	98.2-100.0	100.0-100.0	
Latency of antisaccade (ms)	Median	346.0	357.9	295.4	p=0.9
	(IQR)	(300.7, 371.3)	(288.5, 387.4)	(271.1, 430.2)	
	Range	239.5-558.0	274.4-438.8	264.3-447.7	

A statistically significant difference between the age groups in preterms was present for the antisaccade directional error rate, antisaccade error correction rate and the latency of the antisaccade and in full terms for the antisaccade directional error rate and antisaccade error correction rate. The differences are illustrated in Figure 8.7, Figure 8.8 and Figure 8.9.

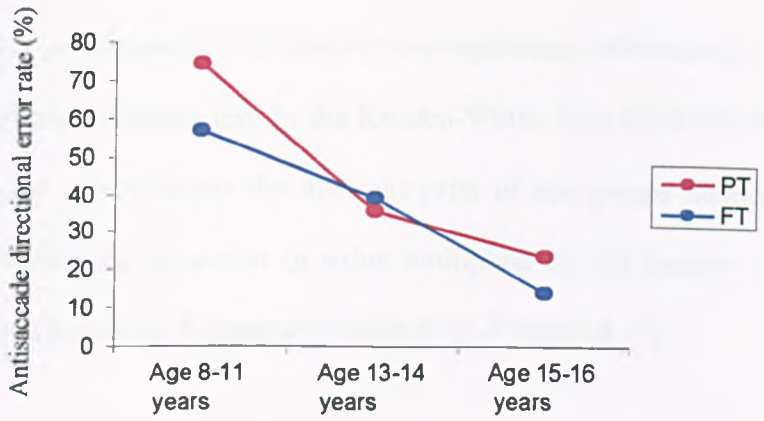


Figure 8.7 Improvement in the antisaccade directional error rate in preterms and full terms at the 3 different age groups

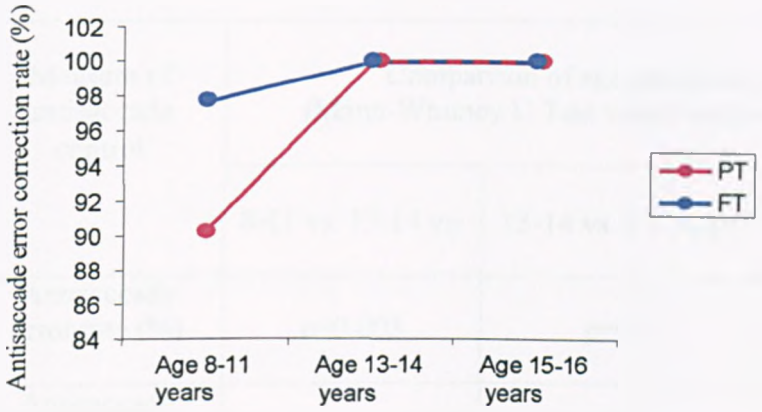


Figure 8.8 Improvement in the antisaccade error correction rate in preterms and full terms at the 3 different age groups

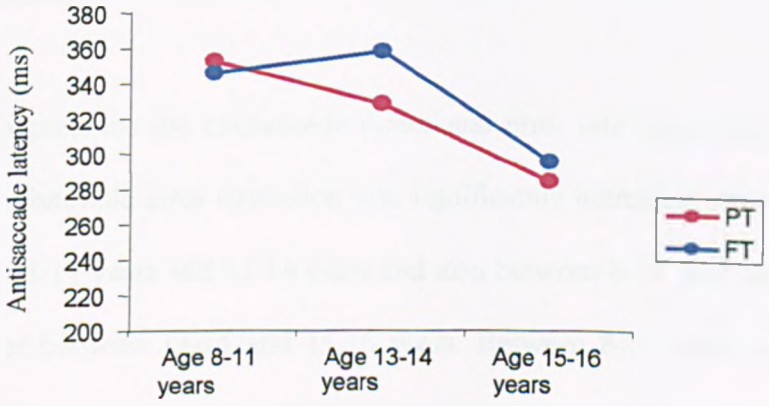


Figure 8.9 Reduction in the antisaccade latency in preterms and full terms at the 3 different age groups

To investigate the location of the significant differences, in the absence of a specific post hoc test for the Kruskal-Wallis Test, the Mann-Whitney U Test was used to investigate the different pairs of age groups including the appropriate Bonferroni correction (p value multiplied by the number of comparisons) for comparison of 3 groups (PT table 8.12, FT table 8.13).

Table 8.12 Comparison of antisaccade measures in preterms between the 3 different age groups, showing the location of the significant differences

Measure of antisaccade control	Comparison of age groups in preterms (Mann-Whitney U Test with Bonferroni correction)		
	8-11 vs. 13-14 yrs	13-14 vs. 15-16 yrs	8-11 vs. 15-16 yrs
Antisaccade error rate (%)	p=0.003	p=0.2	p=0.003
Antisaccade error correction rate (%)	p=0.003	p=1.0	p=0.003
Latency of antisaccade (ms)	p=0.2	p=0.8	p=0.009

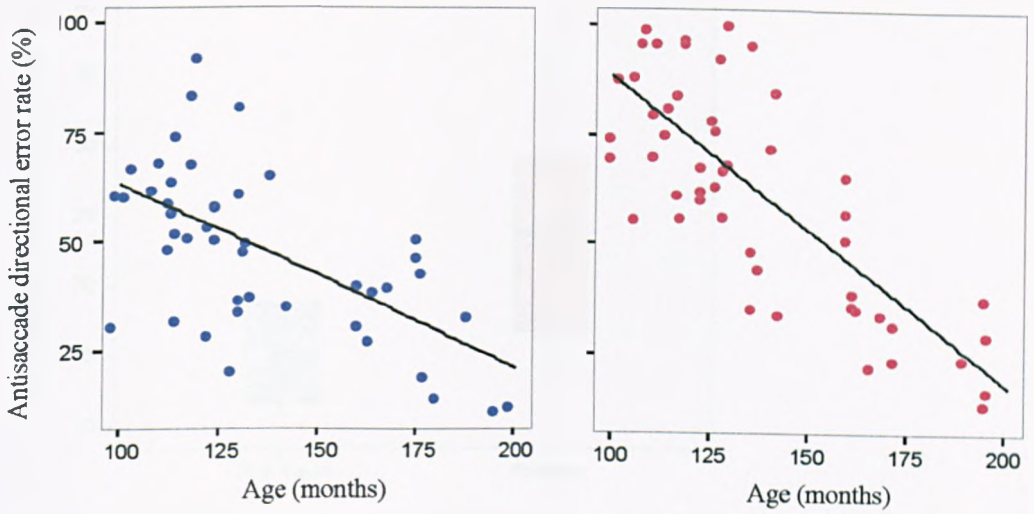
In preterms the antisaccade directional error rate significantly reduced and the antisaccade error correction rate significantly increased, between the age groups of 8-11 years and 13-14 years and also between 8-11 years and 15-16 years, but not between 13-14 and 15-16 years. Between 8-11 years and 15-16 years the latency of the antisaccade also significantly reduced in preterms.

Table 8.13 Comparison of antisaccade measures in full terms between the 3 different age groups, showing the location of the significant differences

Measure of antisaccade control	Comparison of age groups in full terms (*Mann-Whitney U Test with Bonferroni correction*)		
	8-11 vs. 13-14 yrs	13-14 vs. 15-16 yrs	8-11 vs. 15-16 yrs
Antisaccade error rate (%)	p=0.04	p=0.02	p=0.003
Antisaccade error correction rate (%)	p=0.06	p=1.0	p=0.1

In full terms the antisaccade directional error rate significantly reduced across all 3 age groups. Additionally the antisaccade error correction rate increased (and approached significance) between the age groups of 8-11 years and 13-14 years. There were no other significant differences between the age groups in full terms.

To assess if age was predictive of the antisaccade directional error rate, scatterplots (figure 8.10) were produced for all error rate data on preterms and full terms between the ages of 8 years and 16 years (including longitudinal data on subjects that had been retested), and a linear regression performed.



Full term ●
Linear Regression, n=45
Antisaccade error % = 105.1 + (-0.42) * age
R-Square = 0.38
Pearson r = -0.62, p<0.001

Preterm ●
Linear Regression, n=50
Antisaccade error % = 158.5 + (-0.70) * age
R-Square = 0.62
Pearson r = -0.79, p<0.001

Figure 8.10 Scatterplots showing antisaccade directional error rate vs. age in full terms and preterms

Age was shown to be strongly and negatively correlated with the antisaccade directional error rate particularly in preterms, but was statistically significant for both groups. Additionally linear regression showed that the error rate could be predicted by the age of the subject in both groups.

Full terms showed significant reduction within their group in the antisaccade directional error rate through all 3 age ranges unlike preterms where the difference between 13-14 years and 15-16 years was not significant. To assess if there were differences at 15-16 years between the groups of preterms and full terms in the antisaccade directional error rate (figure 8.11) and other measures, both groups were compared using the Mann-Whitney U Test (table 8.14).

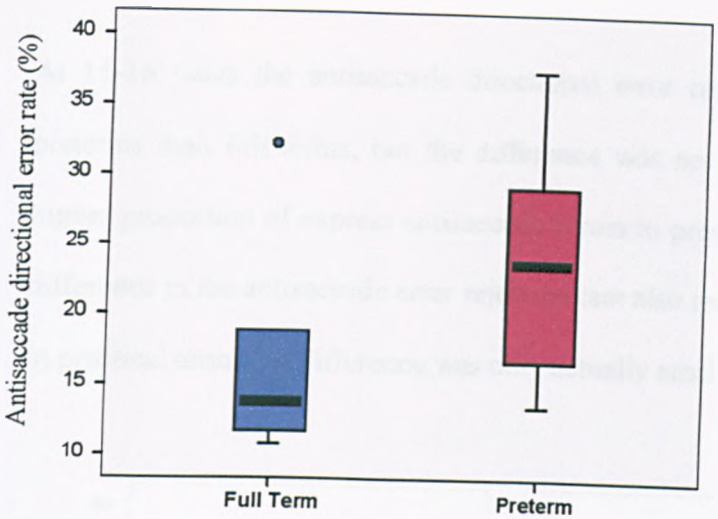


Figure 8.11 Box plot comparing the antisaccade directional error rate in FT and PT age 15-16 years (central black line indicates the median, top and bottom of the box the 75th and 25th percentile, whiskers represent the highest and lowest values that are not outliers, • = outlier more than 1.5 IQR from 75th percentile

Table 8.14 Antisaccade control in preterms vs. full terms at age 15-16 years

Measurement	Descriptive statistics	Preterms (n=5)	Full terms (n=5)	Mann-Whitney
Antisaccade error rate (%)	Median (IQR)	23.7 (15.1, 33.4)	13.8 (11.3, 25.6)	p=0.3
Antisaccade error rejection rate (%)	Median (IQR)	0.0 (0.0, 1.0)	2.1 (1.1, 3.1)	p=0.03
Latency of antisaccade error (ms)	Median (IQR)	186.7 (161.4, 242.2)	207.6 (201.3, 231.0)	p=0.5
Express antisaccade errors (%)	Median (IQR)	10.5 (4.6, 19.6)	0.0 (0.0, 3.9)	p=0.03
Antisaccade error correct'n rate (%)	Median (IQR)	100.0 (100.0, 100.0)	100.0 (100.0, 100.0)	p=1.0
Latency of antisaccade (ms)	Median (IQR)	284.6 (278.1, 311.2)	295.4 (271.1, 430.2)	p=0.7

At 15-16 years the antisaccade directional error rate was slightly higher for preterms than full terms, but the difference was not significant. There were a higher proportion of express antisaccade errors in preterms (figure 8.12) and the difference in the antisaccade error rejection rate also reached significance, though in practical terms the difference was only actually small.

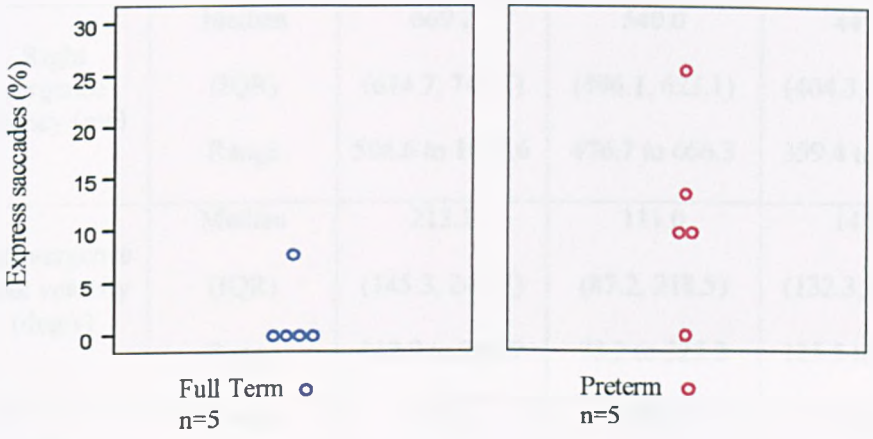


Figure 8.12 Distribution of the proportion of express antisaccade errors in preterm (o) and full term (o) subjects at 15-16 years

8.2iii Vergence data in Experiment 3b (age 15-16 years)

To assess if vergence control had improved with age in preterms and full terms, a comparison was made between all 3 age groups (10-11 years, 13-14 years and 15-16 years) using the Kruskal-Wallis Test. A summary of the vergence measurements for the 3 age groups and statistical significance of any difference is provided in Tables 8.15 (PT) and 8.16 (FT).

Table 8.15 Comparison of vergence measures at ages 8-11, 13-14 and 15-16 years in preterms (Kruskal-Wallis)

Measurement	Descriptive Statistic	Age 10-11 years	Age 13-14 years	Age 15-16 years	Sig.
Left vergence latency (ms)	Median	627.4	563.8	483.6	p=0.003
	(IQR)	(575.0, 733.8)	(493.7, 619.5)	(417.1, 548.9)	
	Range	501.6 to 961.6	477.9 to 675.6	371.4 to 602.1	
Right vergence latency (ms)	Median	669.2	540.0	449.7	p=0.001
	(IQR)	(614.7, 746.7)	(496.1, 623.1)	(404.3, 535.5)	
	Range	506.6 to 1037.6	476.7 to 666.3	359.4 to 563.1	
Left vergence peak velocity (deg/s)	Median	213.1	111.0	145.1	p=0.2
	(IQR)	(145.3, 245.7)	(87.2, 218.5)	(132.3, 273.6)	
	Range	112.9 to 284.9	78.2 to 325.2	125.5 to 273.7	
Right vergence peak velocity (deg/s)	Median	-197.4	-132.7	-101.5	p=0.03
	(IQR)	(-157.1, -259.5)	(-108.7, -181.8)	(-90.9, -178.2)	
	Range	-86.2 to -320.1	-77.9 to -218.4	-88.6 to -216.1	
Left time to peak velocity (ms)	Median	925.5	816.7	678.8	p=0.06
	(IQR)	(739.3, 1095.3)	(625.3, 944.5)	(591.5, 729.9)	
	Range	545.1 to 1188.7	585.7 to 1067.5	557.4 to 755.2	
Right time to peak velocity (ms)	Median	799.8	760.4	737.8	p=0.3
	(IQR)	(726.5, 927.3)	(639.5, 853.6)	(575.5, 832.3)	
	Range	596.9 to 1281.3	559.4 to 1027.3	538.0 to 879.0	
Amplitude of vergence angle (deg)	Median	22.1	19.1	17.7	p=0.4
	(IQR)	(17.0, 25.7)	(14.7, 25.0)	(13.0, 20.5)	
	Range	10.2 to 31.9	4.8 to 31.0	12.6 to 23.1	

Table 8.16 Comparison of vergence measures at ages 8-11, 13-14 and 15-16 years in full terms (Kruskal-Wallis)

Measurement	Descriptive Statistic	Age 10-11 years	Age 13-14 years	Age 15-16 years	Sig.
Left vergence latency (ms)	Median	552.2	493.8	446.9	p=0.2
	(IQR)	(480.1, 595.9)	(461.0, 533.3)	(371.8, 532.5)	
	Range	356.0 to 716.6	347.0 to 571.3	358.1 to 608.4	
Right vergence latency (ms)	Median	530.4	477.7	478.2	p=0.3
	(IQR)	(431.4, 591.5)	(394.8, 533.2)	(390.0, 557.9)	
	Range	390.0 to 619.7	366.7 to 536.9	367.8 to 601.5	
Left vergence peak velocity (deg/s)	Median	218.1	181.8	180.2	p=0.3
	(IQR)	(155.1, 265.7)	(80.5, 221.1)	(132.5, 193.1)	
	Range	75.5 to 321.0	49.6 to 281.5	112.3 to 196.6	
Right vergence peak velocity (deg/s)	Median	-180.0	-173.2	-179.2	p=0.7
	(IQR)	(-137.7, -210.6)	(-134.3, -228.6)	(-149.2, -255.5)	
	Range	-72.3 to -297.8	-87.8 to -254.3	-131.9 to -261.5	
Left time to peak velocity (ms)	Median	848.8	735.5	728.2	p=0.02
	(IQR)	(780.7, 970.2)	(609.6, 820.1)	(575.1, 766.8)	
	Range	643.1 to 1013.0	568.3 to 1076.0	532.8 to 770.2	
Right time to peak velocity (ms)	Median	959.7	615.4	653.3	p=0.01
	(IQR)	(799.7, 1048.3)	(544.1, 776.8)	(632.4, 814.7)	
	Range	605.0 to 1144.8	510.1 to 1098.0	630.4 to 824.0	
Amplitude of vergence angle (deg)	Median	20.4	20.9	24.4	p=0.6
	(IQR)	(17.7, 24.1)	(15.4, 30.5)	(19.1, 27.7)	
	Range	6.0 to 31.6	10.0 to 35.0	16.4 to 29.3	

A significant difference between the age groups in preterms was present for vergence latency (left and right eye), vergence peak velocity (right eye) and time to peak velocity (left eye, borderline) and in full terms for the time to reach peak vergence velocity (left and right eye). The reductions in vergence latency are illustrated in Figure 8.13 and Figure 8.14.

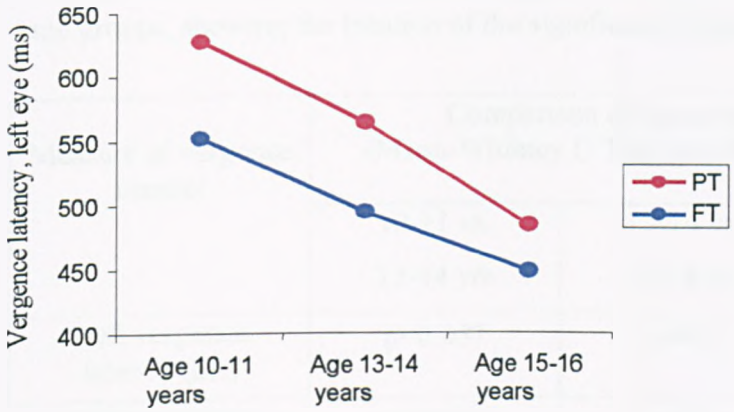


Figure 8.13 Reduction in the vergence latency (left eye) in preterms and full terms at the 3 different age groups

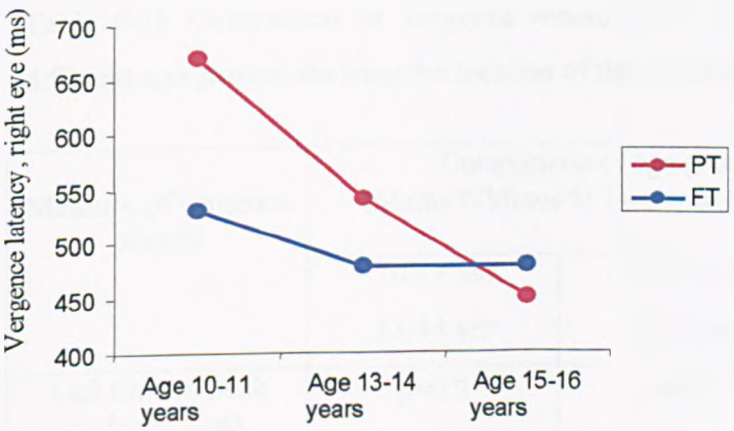


Figure 8.14 Reduction in the vergence latency (right eye) in preterms and full terms at the 3 different age groups

To investigate the location of the significant differences, the Mann-Whitney U Test was used to investigate the different pairs of age groups including the appropriate Bonferroni correction for comparison of 3 groups in both preterms (table 8.17) and full terms (table 8.18).

Table 8.17 Comparison of vergence measures in preterms between the 3 different age groups, showing the location of the significant differences

Measure of vergence control	Comparison of age groups in preterms (Mann-Whitney U Test with Bonferroni correction)		
	10-11 vs. 13-14 yrs	13-14 vs. 15-16 yrs	10-11 vs. 15-16 yrs
Left vergence latency (ms)	p=0.057	p=0.3	p=0.006
Right vergence latency (ms)	p=0.02	p=0.2	p=0.003
Right vergence peak velocity (deg/s)	p=0.09	p=1.0	p=0.2
Left time to peak velocity (ms)	p=0.6	p=0.6	p=0.1

Table 8.18 Comparison of vergence measures in full terms between the 3 different age groups, showing the location of the significant differences

Measure of vergence control	Comparison of age groups in full terms (Mann-Whitney U Test with Bonferroni correction)		
	10-11 vs. 13-14 yrs	13-14 vs. 15-16 yrs	10-11 vs. 15-16 yrs
Left time to peak velocity (ms)	p=0.2	p=1.0	p=0.002
Right time to peak velocity (ms)	p=0.04	p=1.0	p=0.057

Vergence latencies reduced significantly in preterms in the left eye (borderline) and right eye, between the age groups of 10-11 years and 13-14 years and also between 10-11 years and 15-16 years, but not between 13-14 years and 15-16 years. The difference in right peak vergence velocity approached significance between 10-11 years and 13-14 years and the left time to peak velocity no longer reached significance, due to the conservative nature of the Bonferroni correction.

In full terms the time taken to reach peak velocity significantly reduced for the left eye and right eye (borderline), between the age groups of 10-11 years and 15-16 years and also in the right eye between the age groups of 10-11 years and 13-14 years.

Unlike full terms, preterms showed significant reduction in the vergence latency between 10-11 years and 15-16 years. To assess if there were still significant differences between preterms and full terms for vergence latency (figure 8.15) and other vergence measures at 15-16 years, both groups were compared using the Mann-Whitney U Test (table 8.19).

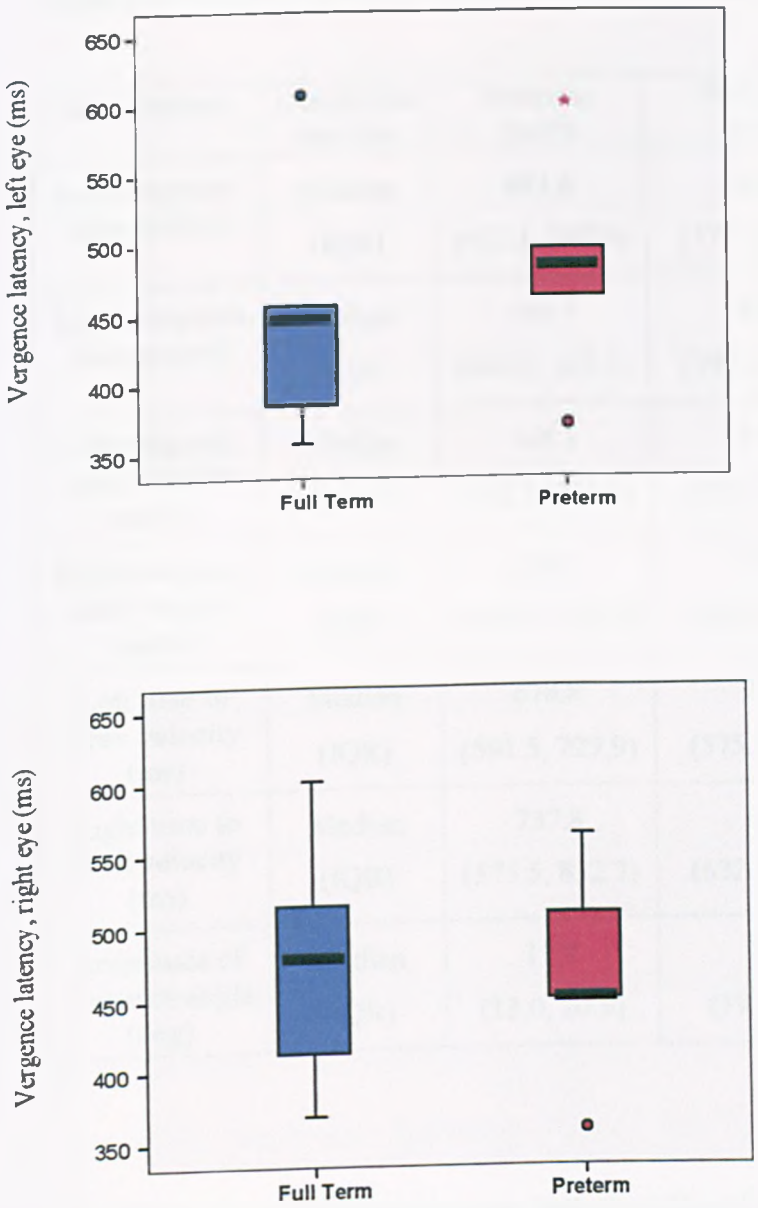


Figure 8.15 Box plot comparing vergence latency (left eye, top; right eye, bottom) in FT and PT age 15-16 years (central black line indicates the median, top and bottom of the box the 75th and 25th percentile, whiskers represent the highest and lowest values that are not outliers, ●● = outliers more than 1.5 IQR from 25th/75th percentile, ★ = extreme outlier more than 3 IQR from 75th percentile.

Table 8.19 Vergence control in preterms vs. full terms at age 15-16 years

Measurement	Descriptive statistics	Preterms (n=5)	Full terms (n=5)	Sig.
Left vergence latency (ms)	Median (IQR)	483.6 (417.1, 548.9)	446.9 (371.7, 532.5)	p=0.4
Right vergence latency (ms)	Median (IQR)	449.7 (404.3, 535.5)	478.2 (390.0, 557.9)	p=0.8
Left vergence peak velocity (deg/s)	Median (IQR)	145.1 (132.2, 273.6)	180.2 (132.5, 193.1)	p=1.0
Right vergence peak velocity (deg/s)	Median (IQR)	-101.5 (-90.9, -178.2)	-179.2 (-149.2, -255.5)	p=0.1
Left time to peak velocity (ms)	Median (IQR)	678.8 (591.5, 729.9)	728.2 (575.1, 766.8)	p=0.7
Right time to peak velocity (ms)	Median (IQR)	737.8 (575.5, 832.3)	653.3 (632.4, 814.7)	p=0.8
Amplitude of vergence angle (deg)	Median (IQR)	17.7 (13.0, 20.5)	24.4 (19.1, 27.7)	p=1.0

At 15-16 years vergence latency in both the left and right eye, was similar for preterms and full terms. There were also no statistically significant differences in the time to reach the peak velocity, the peak velocity or the amplitude of vergence exerted.

8.3 Summary

There were large reductions in the antisaccade directional error rate in both preterms and full terms that had been followed longitudinally over a 3-5 year period. The reduction was particularly marked for the preterm children. Latencies of the antisaccade errors and of the antisaccades also reduced in both groups during this period. At 13-14 years there were no longer any statistically significant differences in antisaccade control between preterms and full terms. At 15-16 years, antisaccade directional error rates had reduced again in both groups, leaving preterms with a slightly higher error rate, though the difference did not reach statistical significance. At 15-16 years preterms also had a statistically significantly higher proportion of express antisaccade errors.

Vergence latencies, in a similar way to the antisaccade error rates, reduced in both groups between 10-11 years and 13-14 years, but at this age were still statistically significantly longer in preterms than full terms. By 15-16 years vergence latencies reduced again in both groups and were now similar with no statistically significant difference. There were no statistically significant differences in any other vergence measures in either age group.

CHAPTER 9: Visual, binocular function and oculomotor assessments in relation to reading ability in children born preterm vs. full term (Experiment 4)

Reading and visual and binocular function data (as described in sections 5.6 and 5.7 respectively) was collected on 36 preterm and 33 full term children (Groups 1 and 2) in addition to the oculomotor data that has been reported in the previous chapters. Both preterm and full term subjects coped well with the tests they were asked to perform. Testing time typically ranged between 50 and 60 minutes, with time for a short break between the orthoptic assessment and reading tests.

9.1 Statistical analysis

The normality of the distribution of the reading (Appendix 2.9) and visual and binocular function data (Appendix 2.10) in preterms and full terms was determined statistically using the Kolmogorov-Smirnov test. Both the reading data and IQ were normally distributed and therefore analysed using parametric tests.

The acuity, near point of convergence, stereopsis, near point of accommodation and prism cover test measurements were not normally distributed and therefore analysed non-parametrically by the Mann-Whitney U Test. An abnormal distribution may have arisen due to the relatively small sample size (Altman & Bland, 1995) which emphasises data that is slightly skewed. The prism fusion range, amplitude of accommodation and accommodative facility measurements were normally distributed however, and were analysed using the unpaired t-test.

9.2 Visual and binocular function assessment in preterms and full terms

Preterms and full terms were compared on the different measures of visual and binocular function using the Mann-Whitney U Test (table 9.1) and t-test (table 9.2) as appropriate.

Table 9.1 Comparison of visual and binocular function assessments in preterms vs. full terms with the Mann-Whitney U Test

Assessment	Descriptive statistics	Preterms (n=36)	Full terms (n=33)	Sig.
Near acuity left eye (LogMAR)	Median (IQR)	0.0 (0.0, -0.02)	0.0 (0.0, -0.02)	p=0.1
Near acuity right eye (LogMAR)	Median (IQR)	0.0 (0.0, -0.02)	0.0 (0.0, -0.02)	p=0.4
Distance acuity left eye (LogMAR)	Median (IQR)	0.0 (0.06, 0.0)	-0.02 (0.0, -0.04)	p=0.001
Distance acuity right eye (LogMAR)	Median (IQR)	0.0 (0.03, 0.0)	0.0 (0.0, -0.02)	p=0.004
Near point of convergence	Median (IQR)	6.0 (6.0, 6.0)	6.0 (6.0, 6.0)	p=0.1
Stereopsis (TNO)	Median (IQR)	60.0 (60.0, 60.0)	60.0 (37.5, 120.0)	p=0.9
Near point of accommodation left (RAF rule)	Median (IQR)	7.0 (6.0, 8.8)	6.0 (6.0, 7.0)	p=0.1
Near point of accommodation right (RAF rule)	Median (IQR)	7.0 (6.0, 8.8)	6.0 (6.0, 7.0)	p=0.1
Near point of accommodation binoc (RAF rule)	Median (IQR)	6.0 (6.0, 7.0)	6.0 (6.0, 7.0)	p=0.2
Prism cover test at near	Median (IQR)	0.0 (0.0, 7.5)	0.0 (0.0, 0.0)	p=0.07
Prism cover test at distance	Median (IQR)	0.0 (0.0, 0.0)	0.0 (0.0, 0.0)	p=0.3

Table 9.2 Comparison of visual and binocular function assessments in preterms vs. full terms with the t-test

Assessment	Descriptive statistics	Preterms (n=36)	Full terms (n=33)	Sig.
Prism fusion range (blur point) at near	mean±sd (range)	35.6±11.5 (18-60)	34.4±11.9 (14-55)	p=0.7
Prism fusion range (break point) at near	mean±sd (range)	45.9±10.8 (22-63)	43.4±13.4 (14-63)	p=0.4
Prism fusion range (blur point) at dist	mean±sd (range)	20.2±6.8 (8-32)	19.4±5.2 (10-30)	p=0.6
Prism fusion range (break point) at dist	mean±sd (range)	23.8±8.3 (12-42)	21.3±6.4 (10-33)	p=0.2
Amplitude of accommodation left eye	mean±sd (range)	5.7±2.2 (1.0-10.5)	6.3±2.2 (3.5-12.5)	p=0.2
Amplitude of accommodation right eye	mean±sd (range)	5.8±2.1 (2.0-10.5)	6.7±3.6 (3.5-13.5)	p=0.2
Accommodative facility left eye	mean±sd (range)	5.4±2.3 (1.0-11.0)	5.6±2.7 (1.0-12.0)	p=0.7
Accommodative facility right eye	mean±sd (range)	5.4±2.2 (1.0-11.0)	5.5±2.6 (1.0-12.0)	p=0.9
Accommodative facility binocularly	mean±sd (range)	5.2±1.9 (1.0-9.0)	5.2±2.6 (1.0-12.0)	p=1.0

Distance visual acuity was slightly, but statistically significantly better in full terms than preterms in both the left eye and right eye, though on average the preterm group still had acuity at a normal level (0.0 LogMAR). Near acuity was similar for both groups in both the left eye and the right eye, with the same median and IQR in preterms and full terms. The proportion of preterms and full

terms where near acuity (table 9.3) and distance acuity (table 9.4) was below normal (worse than 0.0 LogMAR in either eye) was also calculated and analysed using the Chi-squared test (all cells had an expected frequency of >5). Below normal near acuity was present in 12 (33%) preterm children and in 5 (15%) full term children. The difference in proportion of preterms and full terms with abnormal near acuity approached statistical significance (X^2=3.1, p=0.08). Below normal distance acuity was present in 13 (36%) preterm children and in 6 (18%) full term children. Similarly the difference in proportion of preterms and full terms with abnormal distance acuity also approached statistical significance (X^2=2.8, p=0.096).

Table 9.3 Frequency of abnormal near acuity in preterms and full terms

Near acuity below normal	Preterm	Full term	Total
Yes	12 (33%)	5 (15%)	17
No	24 (67%)	28 (85%)	52
Total	36	33	69

Table 9.4 Frequency of abnormal distance acuity in preterms and full terms

Distance acuity below normal	Preterm	Full term	Total
Yes	13 (36%)	6 (18%)	19
No	23 (64%)	27 (82%)	50
Total	36	33	69

Preterms also had slightly higher values on the near prism cover test (approaching statistical significance), which is a measure of the misalignment of

the visual axes that can be latent, manifest or a combination of both. The distribution of the near cover test measurements is illustrated in Figure 9.1.

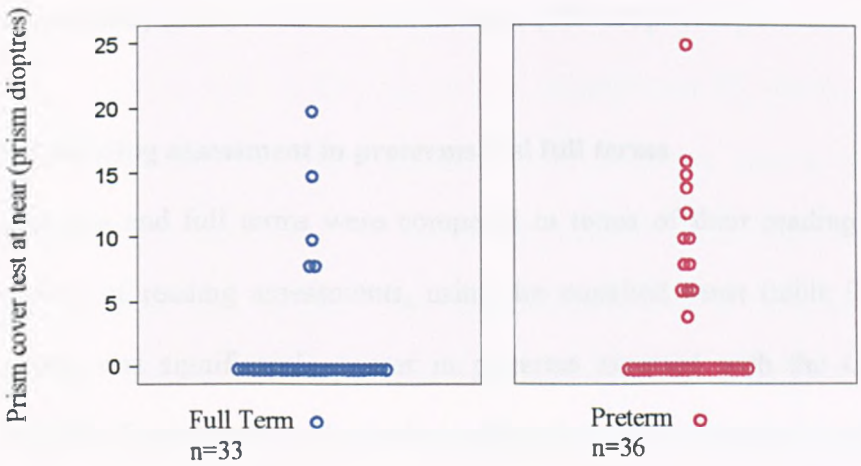


Figure 9.1 Distribution of the prism cover test measurements at near in preterm (o) and full term (o) subjects

The cover test revealed that there were no cases of manifest strabismus in either group, though latent strabismus was present in both. To compare the proportion of latent strabismus (and those with no deviation at all) in preterms and full terms (table 9.5) the Chi-squared test was used (all cells had an expected frequency of >5). All other visual and binocular measures were similar for both groups.

Table 9.5 Frequency of latent strabismus in preterms and full terms

Latent Strabismus	Preterm	Full term	Total
Yes	14 (39%)	5 (15%)	19
No	22 (61%)	28 (85%)	50
Total	36	33	69

Latent strabismus was present in 14 (39%) preterm children (33% exophoria and 6% esophoria) and in 5 (15%) full term children (9% exophoria and 6% esophoria). The proportion of preterms with latent strabismus was statistically significantly greater than that in full terms (X^2=4.9, p=0.03).

9.3 Reading assessment in preterms and full terms

Preterms and full terms were compared in terms of their reading ability on a variety of reading assessments, using the unpaired t-test (table 9.6). Reading ability was significantly poorer in preterms assessed with the Graded Word Reading Test. Preterms also had significantly lower scores for reading accuracy and comprehension, tested with the Neale Analysis of Reading Ability. The speed at which a passage was read, as measured by the reading rate was similar though for both groups.

Table 9.6 Comparison of reading ability in preterms and full terms

Reading Assessment (standardised scores)	Descriptive statistics	Preterms (n=36)	Full terms (n=33)	Sig.
Reading score Graded Word Test	mean±sd (range)	98.1±16.6 (70-130)	106.6±11.1 (80-130)	p=0.01
Reading accuracy Neale Test	mean±sd (range)	98.3±11.9 (79-122)	105.6±11.6 (89-130)	p=0.01
Reading comprehension Neale Test	mean±sd (range)	97.5±11.6 (76-114)	106.0±9.0 (89-130)	p=0.001
Reading rate Neale Test	mean±sd (range)	106.8±10.6 (87-130)	108.2±7.8 (92-120)	p=0.6

Despite significant differences between preterms and full terms, preterm group means were well within (<1SD) normal limits of the standardised normal mean score of 100 on all reading assessments, although the minimum reading scores were much lower than that of full terms. To assess if the group reading scores were lower in preterms because of their overall lower IQ scores, their reading scores and IQ scores were analysed using Pearson's Test to check for the presence of an association between the two measures. Significant correlations for the IQ score were present with the Graded Word Test ($r=0.4$, $p=0.02$) and reading comprehension ($r=0.4$, $p=0.03$) but not with reading accuracy ($r=0.3$, $p=0.1$) or reading rate ($r=0.2$, $p=0.4$). The difference in scores between preterms and full terms on the Graded Word Test and comprehension (Neale Test) therefore likely reflect that the preterm group had an overall reduced IQ in relation to full terms.

To compare the proportion of children with reading difficulties (those who achieved a reading score of 1SD below the mean standardised score, i.e. <85) in preterms and full terms (table 9.7), the Chi-squared test was used (despite a low observed frequency in one cell, all cells had an expected frequency of >5).

Table 9.7 Frequency of reading difficulties in preterms and full terms

Reading Difficulties	Preterm	Full term	Total
Yes	12	1	13
No	24	32	56
Total	36	33	69

Reading difficulties were present in 12 (33%) preterm children and in 1 (3%) full term child. The proportion of preterm children with specific reading difficulties (SRD) was therefore significantly greater that than in full terms (X^2=10.3, p=0.001). To assess if the reading difficulties in the preterms with SRD were related to their IQ, Pearson's test was used to determine the presence of any associations. The IQ in the preterm SRD group was not associated with any of the reading scores (Graded Word Test: r=0.3, p=0.4; comprehension: r=0.4, p=0.2; accuracy: r=0.3, p=0.3; rate: r=0.2, p=0.6). Therefore preterms classed as having SRD with normal IQ (>85), as expected, appear to have reading difficulties that are unrelated to their IQ score.

9.4 Visual and binocular function assessments in preterms in relation to their reading ability

As discussed in Chapter 5 (Methods), only preterms with average IQ (>85) who were also free from major neurological deficits were recruited. Reading problems identified in this cohort could therefore be referred to as specific reading difficulties that could not simply be attributed to an overall cognitive deficit. To assess if the visual and binocular function (table 9.8 and 9.9) performance was associated with the reading difficulties, the results of these assessments were compared in preterms with and without reading difficulties using the Mann-Whitney U Test and unpaired t-test as appropriate.

Table 9.8 Comparison of visual and binocular function assessments in preterms with reading difficulties (RD) vs. preterms without reading difficulties using the Mann-Whitney U Test

Assessment	Descriptive statistics	Preterms with RD (n=12)	Preterms without RD (n=24)	Sig.
Near acuity left eye (LogMAR)	Median (IQR)	0.0 (0.0, -0.02)	0.0 (0.02, -0.02)	p=0.7
Near acuity right eye (LogMAR)	Median (IQR)	0.0 (0.0, -0.02)	0.0 (0.02, -0.02)	p=0.9
Distance acuity left eye (LogMAR)	Median (IQR)	0.0 (0.08, 0.0)	0.0 (0.03, 0.0)	p=0.8
Distance acuity right eye (LogMAR)	Median (IQR)	0.0 (0.06, -0.02)	0.0 (0.0, 0.0)	p=0.9
Near point of convergence	Median IQR	6.0 (6.0, 8.0)	6.0 (6.0, 6.0)	p=0.2
Stereopsis (TNO)	Median (IQR)	60.0 (60.0, 120.0)	60.0 (60.0, 60.0)	p=0.2
Near point of accommodation left (RAF rule)	Median (IQR)	7.0 (6.0, 8.5)	7.0 (6.0, 8.8)	p=0.9
Near point of accommodation right (RAF rule)	Median (IQR)	7.0 (6.0, 8.5)	7.0 (6.0, 8.8)	p=0.9
Near point of accommodation binoc (RAF rule)	Median (IQR)	6.5 (6.0, 7.0)	6.0 (6.0, 7.8)	p=0.9
Prism cover test at near	Median (IQR)	4.0 (0.0, 10.0)	0.0 (0.0, 5.5)	p=0.2
Prism cover test at distance	Median (IQR)	0.0 (0.0, 0.0)	0.0 (0.0, 0.0)	p=1.0

Table 9.9 Comparison of visual and binocular function assessments in preterms with reading difficulties (RD) vs. preterms without reading difficulties using the unpaired t-test

Assessment	Descriptive statistics	Preterms with RD (n=12)	Preterms without RD (n=24)	Sig.
Prism fusion range (blur point) at near	mean±sd (range)	35.2±9.9 (18-53)	35.8±12.5 (20-60)	p=0.9
Prism fusion range (break point) at near	mean±sd (range)	43.3±11.1 (22-55)	47.3±10.7 (30-63)	p=0.3
Prism fusion range (blur point) at dist	mean±sd (range)	21.1±6.5 (11-32)	19.7±7.1 (8-32)	p=0.6
Prism fusion range (break point) at dist	mean±sd (range)	24.1±8.1 (16-42)	23.7±8.6 (12-37)	p=0.9
Amplitude of accommodation left eye	mean±sd (range)	5.8±2.4 (2.5-10.5)	5.6±2.1 (1.0-8.5)	p=0.8
Amplitude of accommodation right eye	mean±sd (range)	6.2±2.5 (2.5-10.5)	5.6±1.9 (2.0-8.5)	p=0.5
Accommodative facility left eye	mean±sd (range)	5.8±2.2 (2.0-9.0)	5.2±2.4 (1.0-11.0)	p=0.5
Accommodative facility right eye	mean±sd (range)	5.9±1.9 (3.0-9.0)	5.2±2.4 (1.0-11.0)	p=0.4
Accommodative facility binocularly	mean±sd (range)	5.3±1.9 (3.0-8.0)	5.2±2.0 (1.0-9.0)	p=1.0

All measures, which encompassed acuity, near point of convergence, fusion range, stereopsis, size of heterophoria and accommodation were similar for preterms with and without reading difficulties, with no statistically significant differences. The interquartile range showed poorer levels of stereopsis with

higher median near prism cover test measurements in preterms with reading difficulties. The distribution of the stereopsis levels and near prism cover test measurements are illustrated in Figures 9.2 and 9.3, respectively.

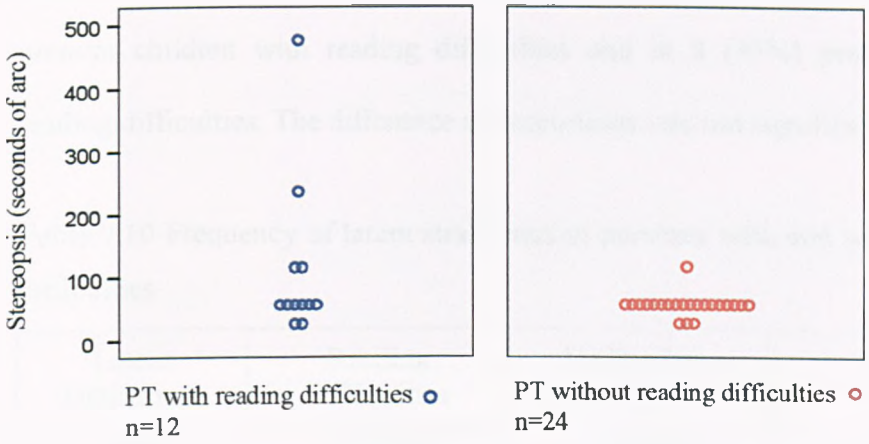


Figure 9.2 Distribution of the stereopsis scores in preterms with (o) and without (o) reading difficulties

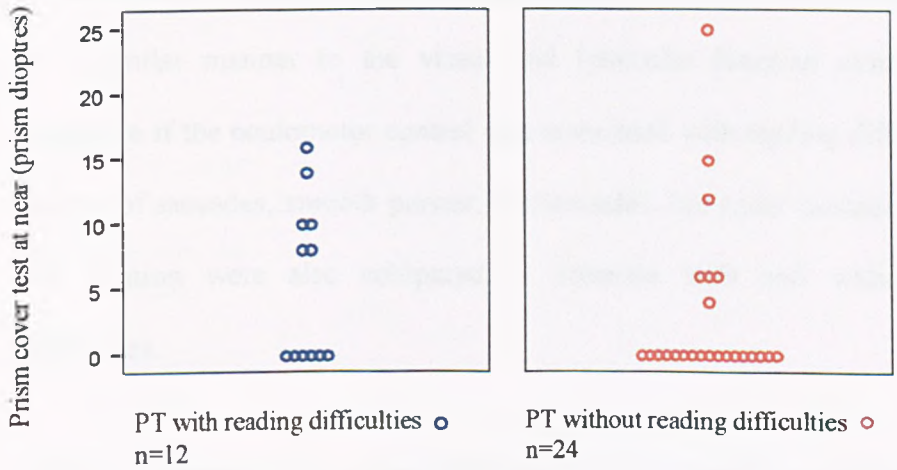


Figure 9.3 Distribution of the prism cover test measurements at near in preterms with (o) and without (o) reading difficulties

To determine if the presence of a latent strabismus was associated with reading difficulties a contingency table was generated using SPSS (table 9.10). This revealed that one cell had an expected frequency of <5 and the data was therefore analysed using Fischer's Exact Test. Latent strabismus was present in 6 (50%) preterm children with reading difficulties and in 8 (33%) preterms without reading difficulties. The difference in proportions was not significant (p=0.5).

Table 9.10 Frequency of latent strabismus in preterms with and without reading difficulties

Latent strabismus	Reading Difficulties	No Reading Difficulties	Total
Yes	6 (50%)	8 (33%)	14
No	6 (50%)	16 (67%)	22
Total	12	24	36

9.5 Oculomotor control in preterms in relation to their reading ability

In a similar manner to the visual and binocular function assessments, to determine if the oculomotor control was associated with reading difficulties, the control of saccades, smooth pursuit, antisaccades, binocular saccades, vergence and fixation were also compared in preterms with and without reading difficulties.

Of the 12 preterms with reading difficulties, 7 were tested as part of Group 1 and therefore data was available for saccades, smooth pursuit and antisaccades, the remaining 5 were tested as part of Group 2 and data was therefore available for binocular saccades, vergence, fixation and antisaccades. As a result of the small

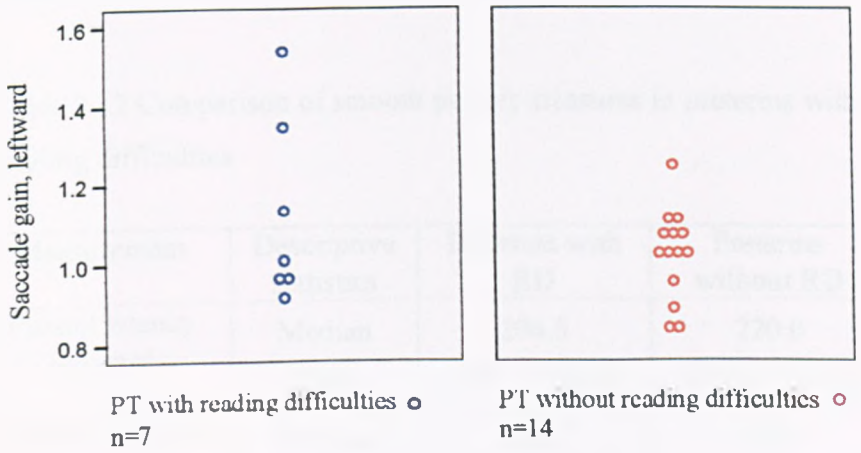
numbers, comparisons on oculomotor control between preterms with and without RD were made using the Mann-Whitney U Test. Comparison of the saccade data (table 9.11) revealed that saccade gain was statistically significantly larger in preterms with reading difficulties, but only for rightward saccades.

Table 9.11 Comparison of saccade measures in preterms with and without reading difficulties

Measurement	Descriptive statistics	Preterms with RD	Preterms without RD	Sig.
Saccade gain leftward	Median (IQR)	1.0 (1.0, 1.4)	1.0 (0.9, 1.1)	p=0.5
Saccade gain rightward	Median (IQR)	1.2 (1.1, 1.2)	1.0 (0.9, 1.1)	p=0.03
Saccade latency leftward	Median (IQR)	197.2 (161.6, 256.9)	200.6 (175.0, 211.6)	p=0.6
Saccade latency rightward	Median (IQR)	228.0 (174.2, 275.6)	209.8 (177.4, 224.6)	p=0.5
Saccade peak velocity leftward	Median (IQR)	-226.6 (-170.0,-322.9)	-230.5 (-204.3,-247.1)	p=0.9
Saccade peak velocity rightward	Median (IQR)	252.0 (214.1, 300.4)	239.0 (193.7, 273.3)	p=0.5
Saccade duration leftward	Median (IQR)	46.4 (43.4, 54.2)	42.4 (39.3, 51.2)	p=0.07
Saccade duration rightward	Median (IQR)	46.6 (43.1, 52.9)	45.0 (38.2, 46.3)	p=0.1
Express saccades (%) of std pro-saccades leftward	Median (IQR)	0.0 (0.0, 17.6)	0.0 (0.0, 8.4)	p=0.9
Express saccades (%) of std pro-saccades rightward	Median (IQR)	4.5 (0.0, 20.0)	4.3 (0.0, 6.4)	p=0.9

The difference in the distribution of saccade gain for leftward and rightward saccades for preterms with and without reading difficulties is illustrated in Figure 9.4. The difference between the groups for leftward saccade duration also approached significance, but the duration was only slightly longer for preterms with reading difficulties. The remaining saccade data showed no differences between preterms with and without reading difficulties.

A



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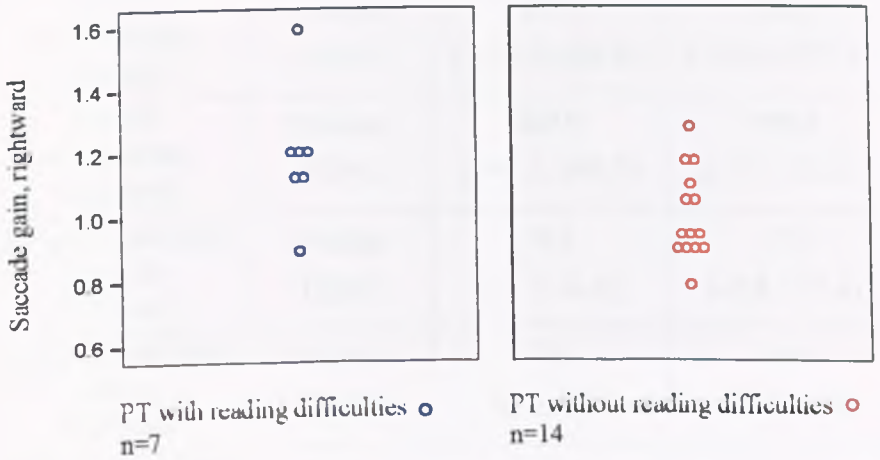

Figure 9.4 Distribution of leftward (A) and rightward (B) saccade gain in preterms with (o) and without (o) reading difficulties

Smooth pursuit data (table 9.12) was also very similar for both groups. Preterms with reading difficulties had slightly shorter pursuit latencies and slightly lower peak slow eye velocities, but the differences for both parameters were minimal and not statistically significant. There were no statistically significant differences between preterms with and without reading difficulties on any of the pursuit data. Comparisons made between the control of antisaccades and vergence in preterms with and without reading difficulties are summarised in Table 9.13.

Table 9.12 Comparison of smooth pursuit measures in preterms with and without reading difficulties

Measurement	Descriptive statistics	Preterms with RD	Preterms without RD	Sig.
Pursuit latency leftward	Median (IQR)	206.5 (191.0, 236.5)	220.0 (188.9, 254.7)	p=0.8
Pursuit latency rightward	Median (IQR)	202.7 (182.7, 232.7)	206.0 (175.2, 223.7)	p=0.8
Pursuit acceleration leftward	Median (IQR)	-197.1 (-149.6,-226.0)	-192.7 (-184.4,-231.7)	p=0.8
Pursuit acceleration rightward	Median (IQR)	204.9 (156.2, 280.7)	190.8 (170.1, 212.7)	p=0.6
Pursuit open loop velocity leftward	Median (IQR)	-9.2 (-7.7, -9.4)	-7.8 (-6.8, -10.4)	p=0.4
Pursuit open loop velocity rightward	Median (IQR)	7.3 (6.5, 8.8)	8.9 (7.3, 9.8)	p=0.2
Pursuit max slow velocity leftward	Median (IQR)	-15.5 (-13.4, -15.6)	-15.7 (-11.4, -18.0)	p=0.8
Pursuit max slow velocity rightward	Median (IQR)	15.4 (12.4, 17.4)	16.5 (13.3, 18.8)	p=0.3

Table 9.13 Comparison of antisaccade and vergence measures in preterms with and without reading difficulties

Measurement	Descriptive statistics	Preterms with RD	Preterms without RD	Sig.
Antisaccade error rate	Median (IQR)	69.3 (56.0, 84.3)	75.0 (63.3, 95.6)	p=0.2
Latency of antisaccade error	Median (IQR)	189.2 (171.8, 207.4)	199.3 (181.6, 222.0)	p=0.1
Express saccade (%) of antisaccade errors	Median (IQR)	20.7 (13.4, 39.3)	8.7 (3.3, 23.5)	p=0.04
Antisaccade error correction rate	Median (IQR)	93.6 (83.3, 99.0)	90.0 (82.8, 95.8)	p=0.4
Latency of antisaccade	Median (IQR)	321.9 (286.6, 368.0)	374.9 (341.4, 419.8)	p=0.007
Vergence latency of left eye	Median (IQR)	621.3 (559.5, 748.7)	634.6 (565.4, 748.8)	p=0.9
Vergence latency of right eye	Median (IQR)	742.0 (600.7, 804.9)	654.3 (606.6, 733.4)	p=0.8
Vergence peak velocity of left eye	Median (IQR)	245.7 (204.8, 261.1)	177.8 (122.5, 218.9)	p=0.09
Vergence peak velocity of right eye	Median (IQR)	-211.5 (-180.5, -270.7)	-186.5 (-110.3, -262.6)	p=0.4
Vergence time to peak velocity in left eye	Median (IQR)	739.3 (591.2, 1010.4)	936.9 (883.3, 1133.2)	p=0.1
Vergence time to peak velocity in right eye	Median (IQR)	799.8 (697.1, 876.2)	789.1 (725.9, 937.2)	p=0.9
Vergence angle	Median (IQR)	22.0 (17.6, 29.5)	22.1 (15.7, 24.3)	p=0.6

Examination of the antisaccade data revealed no differences in the antisaccade error rate in fact preterms without reading difficulties had a higher rate of errors, though the difference was not statistically significant. However, the proportion of antisaccade errors that were express saccades was statistically significantly higher in preterms with reading difficulties (figure 9.5) and the latency of the antisaccades was statistically significantly shorter.

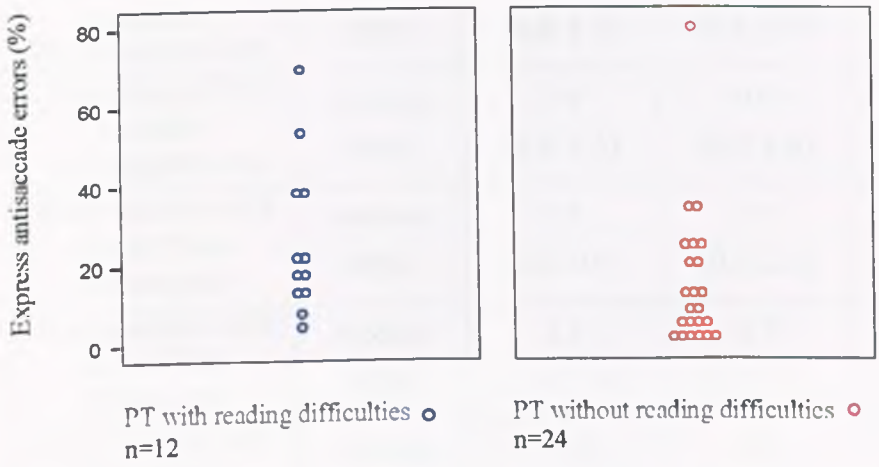

Figure 9.5 Distribution of the proportion of express antisaccade errors (%) in preterms with (o) and without (o) reading difficulties

Vergence control did not differentiate between preterms with and without reading difficulties. The peak vergence velocity was slightly higher for those with reading difficulties, but the differences were not statistically significant.

To assess if disconjugacy or post-saccadic drift was associated with reading difficulties, the binocular saccade data was compared for both groups (table 9.14).

Table 9.14 Comparison of binocular saccade measures in preterms with and without reading difficulties; L=leftward, R=rightward

Measurement	Descriptive statistics	Preterms with RD	Preterms without RD	Sig.
Amplitude of (L) saccadic disconjugacy conv	Median (IQR)	1.8 (0.9, 2.4)	0.9 (0.0, 2.2)	p=0.2
Amplitude of (L) saccadic disconjugacy div	Median (IQR)	0.0 (0.0, 0.5)	1.3 (0.4, 2.5)	p=0.03
Amplitude of (R) saccadic disconjugacy conv	Median (IQR)	0.5 (0.0, 1.7)	1.4 (0.4, 2.5)	p=0.3
Amplitude of (R) saccadic disconjugacy div	Median (IQR)	1.4 (0.8, 3.3)	0.0 (0.0, 1.8)	p=0.2
Post-saccadic drift (L) at 75ms (convergent)	Median (IQR)	0.5 (0.0, 0.9)	1.9 (0.5, 2.3)	p=0.06
Post-saccadic drift (L) at 75ms (divergent)	Median (IQR)	1.5 (1.3, 2.4)	1.7 (0.9, 2.1)	p=0.6
Post-saccadic drift (R) at 75ms (convergent)	Median (IQR)	1.6 (0.6, 3.3)	1.3 (0.4, 2.2)	p=0.9
Post-saccadic drift (R) at 75ms (divergent)	Median (IQR)	0.4 (0.0, 2.5)	1.6 (0.9, 1.8)	p=0.2
Post-saccadic drift (L) at 150ms (convergent)	Median (IQR)	0.5 (0.0, 2.6)	1.7 (0.5, 2.0)	p=0.3
Post-saccadic drift (L) at 150ms (divergent)	Median (IQR)	2.0 (1.2, 4.1)	1.8 (1.1, 2.1)	p=0.5
Post-saccadic drift (R) at 150ms (convergent)	Median (IQR)	1.5 (0.6, 2.9)	1.1 (0.3, 1.9)	p=0.6
Post-saccadic drift (R) at 150ms (divergent)	Median (IQR)	0.6 (0.0, 3.0)	1.7 (0.9, 1.9)	p=0.2

The binocular co-ordination of saccades was generally similar for preterms with and without reading difficulties. In fact preterms without reading difficulties had statistically significantly more saccadic divergent disconjugacy for leftward saccades and a larger amount of post-saccadic convergent drift at 75ms after saccade offset (leftward only). All other binocular saccade data was not statistically significantly different between the two groups.

Finally, the control of fixation was compared between preterms with and without reading difficulties (table 9.15). The frequency of square wave jerks (figure 9.6) was greater in preterms with reading difficulties (approaching statistical significance) and their peak velocity was also statistically significantly higher. The rate of 'other saccadic' intrusions was statistically significantly higher in preterms without reading difficulties, though the difference between the groups was fairly small at only 0.8 per minute. All other measures of the control of fixation were similar between preterms with and without reading difficulties and no other statistically significant differences were present.

Table 9.15 Comparison of fixation measures in preterms with and without reading difficulties

Measurement	Descriptive statistics	Preterms with RD	Preterms without RD	Sig.
Square wave jerk rate per minute	Median (IQR)	10.5 (5.4, 16.3)	5.8 (3.4, 7.0)	p=0.09
Square wave jerk amplitude	Median (IQR)	0.7 (0.6, 1.4)	0.6 (0.4, 0.7)	p=0.1
Square wave jerk peak velocity	Median (IQR)	97.8 (78.5, 178.9)	75.3 (68.7, 93.1)	p=0.05
Square wave jerk duration	Median (IQR)	200.0 (170.3, 224.7)	202.0 (176.9, 267.3)	p=0.7
'Other saccadic' intrusion rate per min	Median (IQR)	0.7 (0.0, 1.1)	1.5 (0.8, 2.8)	p=0.04
'Other saccadic' intrusion amplitude	Median (IQR)	1.7 (0.2, 1.9)	0.7 (0.2, 3.8)	p=0.9
'Other saccadic' intrusion peak velocity	Median (IQR)	123.0 (88.0, 178.0)	130.5 (58.9, 207.3)	p=0.9
'Other saccadic' intrusion duration	Median (IQR)	240.0 (130.0, 255.0)	270.0 (125.0, 456.7)	p=0.5
All saccadic intrusion combined rate per min	Median (IQR)	10.5 (6.1, 16.9)	7.5 (4.2, 10.9)	p=0.2
All saccadic intrusion combined amplitude	Median (IQR)	0.7 (0.6, 1.4)	0.7 (0.4, 1.9)	p=0.6
All saccadic intrusion combined peak velocity	Median (IQR)	106.6 (88.4, 165.5)	91.6 (71.7, 156.8)	p=0.5
All saccadic intrusion combined duration	Median (IQR)	193.0 (165.4, 227.6)	209.5 (170.9, 332.0)	p=0.5

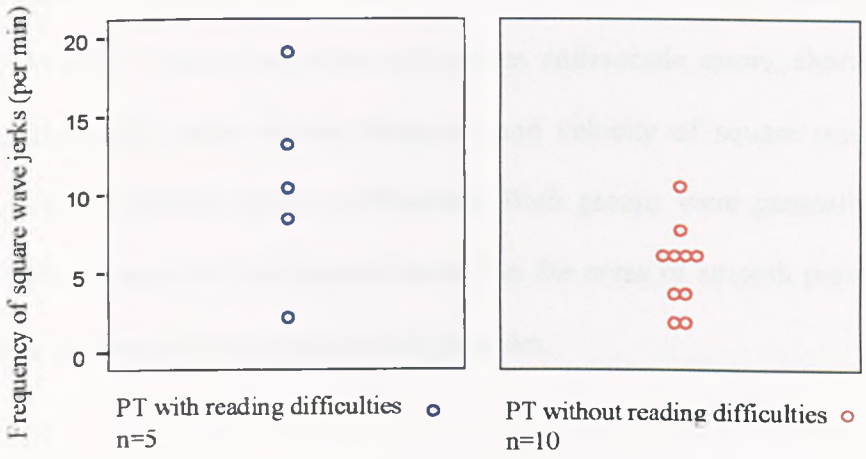

Figure 9.6 Distribution of the frequency of square wave jerks (per min) in preterms with (o) and without (○) reading difficulties

9.6 Summary

The performance of preterms was similar to full terms on most of the visual and binocular function assessments. The main differences were slightly poorer distance acuity, a greater proportion of latent strabismus and subsequently larger measurements on the near prism cover test in preterms. Assessment of the reading ability in preterms revealed that their reading accuracy, comprehension and measure of global reading ability were poorer compared to full terms. To assess if there were any associations between the reading ability and visual and binocular function and oculomotor measures, a comparison was made between preterms with and without reading ability.

Visual and binocular function assessments in preterms with and without reading difficulties showed no statistically significant differences. In terms of oculomotor

control, preterms with reading difficulties had larger saccade gain for rightward saccades, a higher proportion of express antisaccade errors, shorter latency of antisaccades and a higher frequency and velocity of square wave jerks than preterms without reading difficulties. Both groups were generally similar for other measures of oculomotor control in the areas of smooth pursuit, vergence and the binocular co-ordination of saccades.

CHAPTER 10: Discussion

This chapter will discuss the five groups of hypotheses that were outlined in Chapter 5 in relation to the results that have been presented. There will also be discussion of how the findings presented from this study relate to other published research, any weaknesses of the study or improvements that could be made, how these may have affected the results, areas that require further research and implications of the findings.

10.1 Control of saccades

The first group of hypotheses suggested that preterm children would have impaired control of monocular eye movements including saccades, smooth pursuit and antisaccades. Each specific hypothesis will be discussed in turn and this section will discuss saccades. Saccade gain, latency, main sequence relationship and the proportion of express saccades were similar for both preterms and full terms with no significant differences (section 6.2). Additionally, the proportion of preterms with dysmetria (>1SD of the full term mean) was not significantly different to that of full terms. The monocular control of saccades was therefore found to be similar in both preterms and full terms. This is perhaps surprising given the reports of lesions affecting the cerebellum in preterms (Allin et al., 2005, Argyropoulou et al., 2003, Limperopoulos et al., 2005a, Limperopoulos et al., 2005b, Mercuri et al., 1997, Merrill et al., 1998) which, if sufficiently serious, would be expected to cause dysmetria, particularly hypometria and reduced velocity of saccades (Barash et al., 1999, Robinson et

al., 1993). It is possible that the saccade deficits did not arise because the cerebellar lesions in preterms did not affect the saccade related neurones. However, this seems unlikely given that saccade related neurones have been found in the cerebellar vermis (Robinson & Fuchs, 2001) and the vermis was almost always found to be affected in cases of preterm cerebellar infarction (Johnsen et al., 2002, Mercuri et al., 1997). The normality of saccades are also surprising given the reports of thalamic lesions, particularly affecting the pulvinar, and lesions affecting the caudate nucleus and caudate volume. Thalamic lesions could also cause dysmetria and asymmetry due to disruption in the transmission of corollary discharge signals (Bellebaum et al., 2005) and caudate lesions could lead to an increase in latency and a reduction in both the amplitude and velocity of saccades (Kori et al., 1995). The fact that saccade deficits were not found in this study, despite lesions known to compromise the saccadic pathway in preterms may be because of the relatively low incidence of the lesions, which is typically 2.4% for cerebellar haemorrhages (Merrill et al., 1998) and 8.2% for cerebellar infarction (Mercuri et al., 1997). Though the lesions may not be common enough to cause group deficits in preterms, their presence may explain the increased variability and more extreme values that were found in preterms in comparison to the full term controls. It is also possible that lesions occurring very early in life are compensated for due to neural plasticity and development, leaving only very slight or subtle deficits. Another reason why saccade control was similar in preterms and full terms may be because severe lesions in preterms are likely to be associated with cognitive

deficits and reduced IQ (Abernethy et al., 2004, Allin et al., 2001, Inder et al., 2005, Yokochi, 1997), and these cases were excluded in this study. Non-significant findings may also have occurred due to the relatively small sample size. However, the differences in saccade control between the two groups were very small and whilst a very large sample size may be more likely to lead to statistical significance, the differences found in this study can not be considered of clinical significance.

Comparison with other studies is difficult as there is very little published data on the control of saccades in preterm children, other than our own initial findings from this study (Newsham & Knox, 2002) and some studies that did not use quantitative techniques or did not report quantitative data (Jacobson et al., 1998, Salati et al., 2002, Shah et al., 2006b). Jacobson et al (1998) reported that their group of preterms had problems performing normal saccadic eye movements but no specific data was presented. Also the group studied was not typical of preterms, in that all had cerebral palsy and PVL with visual impairment and most had clinically demonstrable nystagmus. Salati et al (2002) reported problems with saccade initiation and co-ordination in children with cerebral visual impairment following perinatal hypoxia, the majority of which were preterm. The severity of the visual deficits, cognitive problems and presence of cerebral palsy again indicated that this group was not representative of preterms generally and differed markedly from the sample used in this present study. Shah et al (2006b) found saccade abnormalities in 10% of preterms, but the nature of the

abnormalities could not be quantified, as eye movements were only assessed qualitatively. This is not dissimilar to the findings of the present study, as although no statistically significant differences were present in the proportion of preterms with dysmetria (>1SD of the full term mean), this may have arisen due to how the dysmetria was defined. In fact the most extreme values for leftward and rightward saccade gain occurred in 2 (10%) preterm subjects (figure 6.2). It is interesting to note that Shah et al (2006b) reported statistically reduced inferior occipital cortical volumes (especially the grey matter) in preterms with oculomotor deficits and this is an area which requires further research with quantitative oculomotor data. The findings of no overall saccadic abnormalities for the preterm group in the present study therefore differed to two studies (Jacobson et al., 1998, Salati et al., 2002) where saccadic deficits were noted in most subjects, though their quantitative nature was not reported. The deficits found in these two studies however, occurred in highly unusual groups of preterms where specific and severe disabilities and anomalies were present and this is likely to account for the difference in the results.

Saccade control in full terms compared well with other studies that investigated children of a similar age. Saccade latencies have been reported to be in the region of 225ms in children at 10-12 years of age (Yang et al., 2002) which is slightly higher but comparable to the full terms in this study (203±32ms, mean±sd). The metrics and dynamics of saccades have been shown to have very little variation between childhood and early to middle adulthood (Munoz et al.,

1998), and the full term peak saccade velocity and duration for a 5° saccade of 230ms and 43ms respectively, were comparable with values expected from the main sequence relationships (Bahill et al., 1975).

Although no differences were found between preterms and full terms in this study on the main sequence parameters, there is scope to undertake further research in this area of saccade control. Saccades were only tested at a single amplitude of 5° which limited the extent to which the main sequence could be assessed. Examining saccade performance at amplitudes of 5°, 10°, 15° and 20° would more effectively allow comparison of the amplitude-velocity relationship. It would also be beneficial to further investigate express saccades, as whilst a high frequency in the overlap task can indicate deficits of fixation control (Biscaldi et al., 1996), it would also be useful to investigate express saccades where they more commonly occur, in the gap paradigm (Fischer & Ramsperger, 1984).

10.2 Control of smooth pursuit

Use of the step-ramp paradigm (Rashbass, 1961) with an unpredictable target direction, allowed investigation of pursuit initiation and the open loop period where there is no visual feedback to guide pursuit. The latency of smooth pursuit was longer in preterms than full terms in both directions, but only reached significance for rightward pursuit. Increased latencies have been found in subjects with degenerative cerebellar lesions (Moschner et al., 1999), though this

is unlikely to be the cause in preterms, as cerebellar lesions would also lead to saccade dysmetria which was not generally evident throughout the preterm group. As well as increased latencies, cerebellar lesions have also been found to cause reduced acceleration during the initiation of pursuit and reduced velocity at the end of the open loop period (Moschner et al., 1999, Takagi et al., 2000). The acceleration of pursuit and open loop velocity were both similar for preterms and full terms, providing further evidence that the cohort of preterms examined in this study did not have any major cerebellar deficits. Increased pursuit latencies have also been shown to occur in subjects with lesions of the posterior parietal cortex (Heide et al., 1996). It is possible that the increased pursuit latencies in preterms may have occurred as a result of diffuse cortical damage leading to a reduced cortical volume (Peterson et al., 2003) and affecting the normal maturation process of the cortex (Rakic, 1988).

The velocities at 0-20ms and 80-100ms after the appearance of the target were measured. As the target was not predictive there should be little or no anticipation and velocity should be close to zero. The velocities were slightly higher in preterms at both epochs, but the differences were not significant. There was little difference between the 0-20ms and 80-100ms epochs, with a very slight increase in leftward velocity and a very slight reduction in rightward velocity, indicating that there was little predictive acceleration between these time points. The slight increase in velocity in preterms at either epoch may therefore be indicative of greater instability of fixation. The control of fixation however, was

tested specifically in a separate experiment and the results will be discussed later. The peak slow eye velocity was also similar in both preterms and full terms and whilst the step-ramp paradigm does not assess pursuit maintenance, normal peak slow eye velocity suggests that the pursuit region of the frontal eye fields was not compromised (Heide et al., 1996) in the preterm group. Further research could be undertaken using predictable targets under steady-state conditions with constant target velocities, to evaluate pursuit maintenance and pursuit gain in preterms. This would allow comparison with the findings of Langaas et al. (1998) who reported significantly reduced pursuit gain in a small sample of eight preterm children who were free from major neurological deficits.

Both preterms and full terms showed substantial variability in all pursuit measures and perhaps this reflects the lack of maturity of the frontal, temporal and posterior cortices that are involved in the processing of pursuit and which only acquire full myelination in early adulthood (Barkovich, 2000, Holland et al., 1986).

As with saccades, comparison of the pursuit findings with other research is difficult due to the paucity of research in this area (Cioni et al., 1997, Jacobson et al., 1998, Langaas et al., 1998, Salati et al., 2002, Shah et al., 2006b), particularly that of a quantitative nature (Langaas et al., 1998). Significant abnormalities of pursuit were reported by Cioni et al. (1997) in preterms with severe and moderate periventricular leukomalacia and poor acuity. The methods however were

rudimentary (though eye movement assessment was not the primary aim of the research), with pursuit assessed by moving a piece of paper with black and white dots at approximately 15deg/s and the sample of preterms differed markedly from the cohort in this study. Pursuit in patients with cerebral visual impairment (64% of whom were preterm) was found to be mildly impaired in 75% and severely impaired in 21% of cases (Salati et al., 2002), though as discussed previously in this chapter the lack of quantitative assessment and a specialised preterm group with cognitive and visual deficits, make comparisons difficult to make with this study. Jacobson et al (1998) noted many preterm children with cerebral palsy, PVL and reduced acuity had difficulty performing smooth pursuit and where pursuit was demonstrated it was notably better to one side than the other. Again, as discussed earlier for saccades, the discrepancies in the reported deficits between their findings and this present study are likely to be due to differences in the selection of preterm subjects and consequently large differences in the type of cerebral and visual deficits suffered. Shah et al (2006b) reported pursuit deficits (direct observation of pursuit interrupted by saccadic refixations) in 21% of preterms, but eye movements were only tested clinically and without a control group. The proportion of preterms with pursuit deficits appears quite high, but could be subject to inaccuracies give the nature by which they were recorded. It is obviously not possible to compare different parameters of pursuit control with the present study. Only one study quantitatively assessed pursuit in preterms (Langaas et al., 1998). However the study used a predictive target and therefore there was no data available on pursuit initiation. There were

also differences in the speed of the target, which at 17deg/s was slightly faster than that used in this study (14deg/s). Langaas found that a small sample of 8 preterm children had reduced pursuit gain (0.81±0.13, mean±sd) in comparison to full term controls (1.03±0.14, mean±sd). This may be considered slightly contradictory in that the present study found no difference in maximum slow eye velocity between preterms and full terms, but there are clearly substantial methodological differences, particularly in the task used and subsequently in the neural control involved in the maintenance rather than the initiation of pursuit. It was not possible to compare the acceleration and latency of smooth pursuit in full terms with other research as no studies were found that had used a step-ramp paradigm to investigate pursuit initiation in children, though several had investigated pursuit maintenance (Accardo et al., 1995, Haishi & Kokubun, 1995, Mezzalira et al., 2005, Ross et al., 1993). Pursuit latency has been shown to reduced in infancy up to 6 months of age (Jacobs et al., 1997), but beyond that little has been published and this is an area that requires further research.

10.3 Control of antisaccades

The antisaccade directional error rate was significantly higher in preterm children compared to full terms. Additionally, the mean latency of the antisaccade error was shorter and there were a higher proportion of express antisaccade errors (both approaching significance) in preterms. The antisaccade errors were also corrected less frequently in preterms but although the difference was statistically

significant, the discrepancy was very modest at only 4.5%. The antisaccade latencies were similar for both groups.

The successful execution of an antisaccade has two components. The first is to suppress the reflexive prosaccade when a new target is introduced and secondly a voluntary saccade must be generated in the opposite direction. The antisaccade error correction rates, although very slightly lower in preterms, were still high at 89.1% indicating that they did not have difficulty in generating the voluntary saccade. This is also true for the full terms who corrected 93.6% of the antisaccades. The reason for relatively high error rates in both groups was most likely due to difficulties in inhibiting the reflexive saccade. Determination of the nature of the antisaccade error allows inference to be made regarding the location of the neural deficit. The errors were likely to be as a result of a deficit in the region of the dorsolateral prefrontal cortex (DLPC), which has an important inhibitory role with connections to the posterior parietal cortex and superior colliculus (Ford et al., 2005) and lesions of the DLPC have been shown to cause increased error rates (Pierrot-Deseilligny et al., 2003). Also the fact that the errors were corrected, implies that the frontal eye fields responsible for voluntary saccades (Pierrot-Deseilligny et al., 2002) were relatively unaffected. This interpretation is also consistent with the other saccade and pursuit data.

The error rates as discussed in Chapter 2 have been found to be increased in children, reducing rapidly between the ages of 8-15 years (Fukushima et al.,

2000, Munoz et al., 1998). Full term error rates of 54.2% at age 10 years compared well with others, lying in between the level of 65% (Fischer et al., 1997) and 30% (Munoz et al., 1998) that have been reported at this age. It is thought that the reason for the high error rates in children and reduction towards adulthood is due to the initial immaturity and subsequent myelination and development of the frontal cortex (Anokhin et al., 1996, Luna & Sweeney, 1999). The reason for higher error rates in preterms may therefore be due to a lesion in the area of the DLPC, a diffuse lesion affecting the frontal cortex or perhaps a delay in the maturation of the frontal cortex. This could lead to a permanent deficit, slower development of this aspect of oculomotor control or a combination, with a longer developmental period in preterms and a permanent residual deficit. This will be addressed by the longitudinal and cross-sectional data that was collected in preterms and full terms at the ages of 13-14 and 15-16 years. It is not really surprising that preterms could be at risk from this type of delayed maturation of oculomotor control. Even in the majority of preterms where IQ is within the normal range, they often have delayed development with numerous deficits in areas such as motor control, aspects of cognitive ability, behavioural problems (Fily et al., 2006, Foulder-Hughes & Cooke, 2003) and of particular relevance to antisaccades, deficits in executive function which is under the control of the prefrontal cortex (Anderson & Doyle, 2004, Taylor et al., 2004). It is thought that deficits in executive function in preterms may be related to periventricular leukomalacia (Anderson & Doyle, 2004), where early white matter damage may impair later myelination and development of grey matter

structures (Inder et al., 1999). Even if insults such as PVL and IVH are not present, the rapid 4-fold increase in grey cortical matter during the third trimester (Huppi et al., 1998) makes cortical development particularly vulnerable to insults, and probably explains the reduction in overall cortical volume that has been reported in preterms (Inder et al., 2005, Peterson et al., 2003). It would be useful to conduct further research investigating any association between executive function and antisaccade error rate in preterms and also to assess the extent to which preterms have volumetric or functional alterations in the area of the DLPC using functional MRI techniques.

In terms of antisaccade control, the increased directional error rate was clearly the main area of deficit that was found in preterms. However, preterms also tended to have shorter latencies of the antisaccade errors and a higher proportion of express antisaccade errors. Similarly, in prosaccades increased activity of the FEF has been found to be associated with reduced saccade latency, increased proportion of express saccades and an increased antisaccade error rate (Everling & Munoz, 2000). The difference in error latency and proportion of express antisaccade errors between preterms and full terms may therefore provide further indication of a deficit in the area of the frontal lobe and perhaps disruption of the balance between inhibition and the generation of saccades. However, the increased proportion of express antisaccade errors in preterms only approached statistical significance and there was considerable variability within the preterm

group on this measure. This conclusion must therefore be viewed with caution until further research, particularly using both overlap and gap tasks, is performed.

The main areas of deficit of antisaccade control in preterms (directional errors, proportion of express antisaccade errors and antisaccade error correction rate) were analysed in relation to GA using linear regression. The GA was not found to be predictive of any of the antisaccade measures. This result again needs to be viewed with caution however, because the range of GA was necessarily quite small, with the majority of preterms having GA's between 29 and 32 weeks. This makes it difficult to find statistically significant associations. Further research could be undertaken with greater numbers of preterm children with GA's down to 26-28 weeks, which would provide a larger range and more effectively investigate if antisaccade control was in fact progressively poorer in children born with greater prematurity.

Unfortunately it was not possible to compare the control of antisaccades in preterms with other studies, as no other research was found in this area. The mean latency of the antisaccade errors in full terms was 212ms (with most subjects between 150ms and 250ms) which compares well with Munoz et al. (1998) where at age 9-11 years most subjects had latencies between 125ms and 275ms. The mean latency of the antisaccade in full terms was longer than the latency of the antisaccade error, which has also been consistently reported in other studies (Fischer et al., 1997, Klein & Foerster, 2001, Munoz et al., 1998).

The magnitude of the antisaccade latencies in full terms (353ms) compares well other children (311ms) of a similar age (Klein & Foerster, 2001). The antisaccade data in full terms was therefore similar to that reported in other studies.

10.4 Directional differences

No significant directional differences in preterms or full terms were found in this study for either saccades or antisaccades. This is contradictory to other studies where directional asymmetries have been reported (Honda, 2002, Munoz et al., 1998, Weber & Fischer, 1995). However, the differences found by Munoz et al. (1998) although reaching statistical significance due to their large sample size, were fairly modest at 2.4% for antisaccade directional errors, 6°/s for peak velocity and 2.6ms for duration in standard prosaccades. The reason why directional differences were not found in the present study may be because a synchronous rather than a gap paradigm was used. This has been found to reduce asymmetries in some studies (Weber & Fischer, 1995), although not in others (Honda, 2002).

10.5 Summary of findings in relation to the first group of hypotheses

The control of saccades in preterms as a whole did not significantly differ to that of full terms and therefore the hypothesis that preterms have impaired control of saccades was rejected. It should be noted however that preterms tended to have more extreme values and further research will determine if there is just a

proportion of individuals born preterm who have saccadic deficits. The hypothesis that preterms have impaired control of smooth pursuit could not be entirely rejected as pursuit latency was longer in preterms, although the difference was fairly modest. Also this study used a step-ramp paradigm to assess pursuit initiation and therefore no information about the maintenance of pursuit was available. Antisaccade error rates were significantly higher in preterms with a tendency for shorter latencies of the antisaccade errors and a higher proportion of express saccades. The hypothesis that preterms have impaired control of antisaccades was therefore accepted.

10.6 Control of binocular saccades

The second group of hypotheses predicted that preterm children would have impaired binocular co-ordination, vergence and fixation in comparison to full terms. This section will address the first of these hypotheses, in relation to the control of binocular saccades.

As discussed in Chapter 3, at the beginning of a saccade the eyes are not perfectly conjugate (Collewijn et al., 1988) and the extent and direction of the disconjugacy varies during childhood (Fioravanti et al., 1995). In the present study no differences were found between preterms and full terms in the amounts of convergent or divergent saccadic disconjugacy, for either leftward or rightward saccades. It was not possible to compare the saccadic disconjugacy and

post-saccadic drift in preterms with other results as no other research has been undertaken in this area.

Saccadic disconjugacy in full terms ranged from 0.8° to 1.6°, depending on the direction of the saccade and type of disconjugacy. This compares well with Yang and Kapoula (2003) who reported the overall level of disconjugacy in children aged 10-12 years at 1.3° and 0.8° for fixation at a near (20cm) and distance (150cm) target, respectively. The maximum amount of saccadic disconjugacy in other studies (Fioravanti et al., 1995) of about 4° is also very similar to the maximum of 3.9° found in the full term group. Any discrepancies that occurred between the studies are likely to be as a result of differences in the fixation distance, which has been shown to affect the amount of disconjugacy (Yang & Kapoula, 2003). The type of disconjugacy in children aged 5-9 years has been found to be predominantly convergent, and becoming divergent, the same as found in adults, by the age of 11-13 years (Fioravanti et al., 1995). This is similar to the findings of full terms in the present study, where they appeared to be in a transition period from convergent to divergent disconjugacy, with the proportion of divergent saccadic disconjugacy at 37% and 51% for leftward and rightward saccades, respectively. These values were lower however than the proportion (72%) found by Yang & Kapoula (2003) in children age 10-12 years (mean age was not provided in the study). This may be due the fact that the full term group was slightly younger (range 10-11 years, mean 10 years 10 months) and was

therefore still displaying some convergent disconjugacy typical of younger children.

Post-saccadic drift was similar in preterms and full terms with no significant differences. The mean amount of drift in full terms ranged from 0.9° to 1.6°, which was somewhat greater than the amount (0.7°) found by Yang & Kapoula (2003) in 10-12 year olds. However, the authors reported a large reduction in the amount of drift in childhood which reached adult levels by 10-12 years. The differences may therefore have been due to a combination of the rapid development that occurs in children and the fact that the full term group were of a slightly younger age than the group used by Yang and Kapoula. There were also notable differences between the studies in the fixation distance used (57cm vs. 20cm) and the separation of the saccade targets (5° vs. 20°). In addition there was considerable variability between individuals in both studies and the number of 10-12 year old subjects recruited by Yang and Kapoula was particularly low at only four.

It is a little surprising that the preterm children did not have any significant differences to full terms in their binocular co-ordination of saccades given the increased prevalence of strabismus (Cooke et al., 2004, O'Connor et al., 2002b) and reduced levels of stereopsis (Cooke et al., 2004, Hard et al., 2000) that have been reported in preterms. It is accepted though that the measurement of the binocular control of saccades assessed the dynamic co-ordination of the eyes,

which was purely a measure of their relative spatial position and did not assess fusion. This is clearly different to the static assessments of binocular vision, alignment and stereopsis where deficits have been reported (Cooke et al., 2004, Hard et al., 2000, O'Connor et al., 2002b). However, an association between dynamic co-ordination and static alignment has been reported, where large amplitudes of saccadic disconjugacy and post-saccadic drift have been found in subjects with strabismus (Kapoula et al., 1997). The poor binocular co-ordination of saccades found by Kapoula et al. was mostly in subjects with large angle strabismus with no binocular vision, rather than those with very small angle strabismus and some binocularity. The reason why preterms in the present study did not show any deficits in the binocular co-ordination of saccades was probably because there were no instances of manifest strabismus in this cohort (despite the increased risk of strabismus in preterms as a whole) and because impairments in saccadic disconjugacy and post-saccadic drift only tended to occur with more severe deficits of binocular vision.

10.7 Control of vergence

Vergence latency, peak vergence velocity, time to peak velocity and the amplitude of the vergence angle were measured and compared between preterms and full terms. The vergence latency was significantly longer in preterm children, though the peak velocity, time to peak velocity and vergence angle showed no significant differences between the groups.

As discussed in Chapter 3, increased vergence latencies have also been found in young children, and this aspect of vergence control appears to have quite a long developmental period (Yang et al., 2002). At age 10-12 years, Yang et al. (2002) found vergence latencies had reduced steadily from 4.5-6 years, to a level of 230ms. This is far lower than the level found in the present study for full terms of 540ms for the left eye and 515ms in the right eye. The large discrepancies are likely to be due to methodological differences. One important difference was that Yang et al. introduced a target as the cue for vergence, whereas in this study the cue was the removal of the fixation target which then required a vergence movement to a target already in position. The introduction of a vergence target in the study by Yang et al. is likely to have produced a greater stimulation to converge which more closely resembles normal everyday conditions and is likely to explain the shorter latency. Additionally there were differences in the type of target used. Yang et al. used an LED which does not have an accommodative component and therefore the vergence would be driven by disparity. The target used in the present study was accommodative and would therefore be additionally driven by blur. Vergence latencies for blur-driven stimuli have been found to be longer than those that are disparity driven (Leigh & Zee, 2006). It may be useful to conduct further research to investigate the effects of vergence to separate stimuli of blur and disparity. The effect of a blur stimulus in isolation can be assessed by assessing vergence monocularly to an accommodative target. This allows different components of vergence to be assessed, but clearly does not

assess the control of vergence in a natural environment, as was achieved in this study, where both blur and disparity stimulated vergence movement.

As indicated earlier (Chapter 3) the frontal cortex (in the prearcuate region) has been reported to be an important area involved in the control of vergence (Gamlin & Yoon, 2000) and it is thought that the long developmental period of vergence latency is associated with the long maturation period of the frontal cortex (Yang et al., 2002). This is interesting given the deficits found in antisaccade control in the preterm children in this study, which may also be attributable to deficit of an area of the frontal cortex, the DLPC. However when the association between vergence latency and antisaccade directional error rate was assessed, the correlation was only moderate ($r=0.4$) and did not reach statistical significance. This non-significant result could be attributable to the fact that there were only 15 subjects, which reduces the chance of a significant result and makes assessing the presence of a true correlation difficult. It would be useful therefore to investigate this further in order to increase the sample size and also assess another group of preterms with a modified task where the cue to execute vergence was the appearance of a target which would allow better comparison with other studies. Although vergence latency was longer in preterms at age 10-11 years, in a similar way to the problems with antisaccade control, vergence initiation could improve in line with maturity of the frontal cortex and eventually reach normal levels, or alternatively fail to improve at all resulting in a permanent deficit, or perhaps improve slightly leaving a residual deficit. The

research in this study investigating preterms at older ages aimed to address these issues and will be discussed later. To assess if the increased vergence latency was associated with the degree of prematurity and length of GA, both variables were analysed to assess the presence of a correlation. Although the correlation was stronger for the left eye, neither was statistically significant. This may be attributable again to the small sample size or perhaps the range of GA was insufficient to demonstrate a significant correlation. Alternatively, once prematurity has exceeded a specific level, the amount of deficit in vergence control may reach a threshold beyond which a shorter GA does not cause any further increase in deficit.

The mean peak vergence velocity in the full term group was in the region of 207deg/s which compares well with the finding of 219deg/s by Yang and Kapoula (2004). Others though have found much lower velocities in the region of 70deg/s (Hung et al., 1997). The target position in the study by Hung et al. however required much smaller amplitudes of vergence (15deg) to be executed than the present study. This could account for the discrepancy in velocities as the peak velocity-amplitude relationship has been shown to fall on a main sequence in a similar way to that of saccades (Hung et al., 1994). Preterms did not show any differences to the full terms in the ability to execute the amplitude of vergence or reach the peak vergence velocity. Integrity of these aspects of vergence control in preterms therefore indicates that there were unlikely to be major deficits in the area of the midbrain, specifically in the region of the

supraoculomotor area, which as discussed in Chapter 3 (Mays, 1984, Mays et al., 1986) contains cells that discharge in relation to the vergence angle (vergence tonic cells), vergence velocity (vergence burst cells) and to both vergence angle and velocity (vergence burst-tonic cells). Additionally, there is further evidence that the preterms investigated in the present study did not have any major cerebellar lesions, which as well as saccade and pursuit performance would also be likely to compromise vergence amplitude (Gamlin, 2002, Westheimer & Blair, 1973). Unfortunately, it was not possible to compare the vergence control of the preterms with other studies, as again no other research has been found in this area.

10.8 Control of fixation

The control of fixation was determined initially by measurement of the saccadic intrusion rate (for all SI's combined, SWJ and other SI's). The rate of saccadic intrusions was no higher in preterms compared to the full term controls. This was investigated in more detail (in both preterms and full terms) by correlating the different categories of saccadic intrusion with both the antisaccade directional error rate and proportion of express antisaccade errors. There were no significant correlations present for either preterms or full terms. These findings were surprising given the difficulties encountered by the preterm group during the antisaccade task, which indicated a deficit in the inhibitory control of reflexive saccades. It follows that if there are difficulties in preventing unwanted saccades, there might be a higher rate of saccadic intrusions and a positive correlation between this and the antisaccade error measures. As discussed earlier, small

samples can sometimes make it difficult to achieve significant correlations and it is possible that this is why the correlation between the SWJ rate and proportion of express saccades did not reach significance. However, the correlation coefficients were generally very low and a larger sample is unlikely to have affected the conclusions. The coefficient for the correlation between the 'other saccadic' intrusions category and the antisaccade error rate was slightly higher than the rest of the categories at 0.4, but is unlikely to be of interest as the rate of the intrusions was only very low at 1.9 per minute and the rate was actually higher in full terms. A lack of an association between antisaccade performance and the rate of saccadic intrusions has also been found in normal adult subjects (Gowen & Abadi, 2005). The authors concluded that saccadic intrusions seem be related to the control of attention rather than the voluntary control of saccades. The fact that the DLPC does not appear to play a role in the production of saccadic intrusions, would explain the lack of correlation found in the present study between antisaccade performance and the SI rate in both preterms and full terms. The rate of all SI per minute in full terms (9.1±3.4, mean±sd) was lower than the rate (18.0±14.3) found by Abadi & Gowen (2004) though as can be seen by the standard deviation, even in normal subjects there is considerable variation in the mean. Also methodological differences were present, with their study having a much larger age range, greater viewing distance and longer duration of fixation task which could perhaps lead to spells of reduced attention and thus more SI's (Gowen et al., 2005, Herishanu & Sharpe, 1981). The SWJ rate was also lower in full terms (6.5±3.7, mean±sd) compared to that of 11.5±11.6 found

by Abadi and Gowen, but was similar to the rate found by others of 8.9±4.9 (Shaunak et al., 1999). Again differences between the studies may well have arisen due to the natural variability that has been found to occur in normal subjects.

In terms of the main sequence parameters, the peak velocity, amplitude and duration measurements in preterms and full terms were generally similar for all saccadic intrusions combined and the 'other saccadic' intrusion categories, though for SWJs the duration was found to be significantly longer in preterms. The SWJ velocity was also lower in preterms but this did not reach statistical significance. This is contradictory to the assessment of reflexive saccades where the duration and peak velocities were similar for preterms and full terms, but may reflect differences in the processes involved in the generation of SI's and reflexive prosaccades. The main sequence relationship between peak velocity and amplitude for SWJs and 'other saccadic intrusions' showed a significant linear correlation in both preterms and full terms, demonstrating that the intrusions were of a saccadic nature; this is similar to that reported by Abadi & Gowen (2004). As with other oculomotor measures it was not possible to make comparisons between the findings of the preterm group and other studies as no other research has been undertaken in this area.

10.9 Summary of findings in relation to the second group of hypotheses

The binocular co-ordination of saccades was similar in preterms and full terms, despite the increased risk of binocular vision problems in preterms. However,

this may be due to the low risk nature of the preterm cohort used in this study. The hypothesis that preterms have impaired binocular co-ordination of saccades was therefore rejected. In addition to deficits of antisaccade control, the other main defect of oculomotor control found in preterms in this study was in the area of vergence initiation indicated by significantly increased vergence latencies. The hypothesis that preterms have impaired control of vergence was therefore accepted. The remaining hypothesis was in relation to fixation. The control of fixation was generally similar for preterms and full terms, but the mean duration of square wave jerks was longer in preterms and therefore the hypothesis that preterms have impaired control of fixation could not be entirely rejected. It would be useful to conduct further research in this area assessing control over longer durations of fixation and with a larger sample of subjects.

10.10 Development of the control of antisaccades and vergence – assessment at 13-14 years

The third group of hypotheses stated that preterm children have impaired development of eye movement control in the areas of antisaccades and vergence at 13-14 years of age. This section will address each hypothesis in turn.

10.10i Development of antisaccades at age 13-14 years

Antisaccade control was assessed longitudinally in both preterms and full terms. This revealed that in preterms the antisaccade directional error rate and latency of the antisaccades had significantly reduced and a significant improvement had been made in the antisaccade error correction rate. The reduction in the

antisaccade directional error rate for full terms, though present, was smaller and did not reach significance. However, the lack of significance was probably as a result of a Type II error, where the null hypothesis is falsely accepted. This is likely to have occurred because of difficulties recruiting full terms for a second visit, making the sample of full terms very small at just 3 subjects. For this reason an alternative method of analysis was used where the control of antisaccades was compared using cross-sectional data from those seen at age 8-11 years and those seen at 13-14 years, thereby increasing the sample size. The directional error rate again showed a reduction, (though was slightly smaller than in the previous analysis) and this time easily reached statistically significance ($p=0.01$). Both preterms and full terms therefore showed significant improvement in the voluntary control of saccades, demonstrating a reduction in the antisaccade directional error rate from the age of 8-11 years to 13-14 years. This was certainly expected for the full terms, where as discussed earlier in this chapter, rapid improvements in the error rates have been found to occur between the ages of 8-15 years (Fukushima et al., 2000, Munoz et al., 1998). The level of 39% errors for the full terms in this study was slightly higher, but similar to the level found by Fischer et al. (1997) which was just over 30% (the data was presented graphically and a precise value was not provided for this age group). Unfortunately there is no data published on preterm subjects for comparison.

For other aspects of antisaccade control, analysis of the cross-sectional data showed similar results to the longitudinal data for preterms, with significant

(borderline) reduction in the latency of the antisaccade and a significant increase in the antisaccade error correction rate. For the full terms, unlike the longitudinal data, a small but significant increase was revealed in the antisaccade error correction rate. The improvement in the correction rate between the age groups of 8-11 years and 13-14 years is likely to be due to an improvement in the voluntary control of saccades, particularly the component of the antisaccade task that requires the generation of a voluntary saccade, which is under the control of the FEF (Pierrot-Deseilligny et al., 2002) and as discussed previously, is part of the frontal cortex that is still maturing during this period (Anokhin et al., 1996, Luna & Sweeney, 1999). Unlike preterms, full term children did not show a significant reduction in the latency of the antisaccade, which would have been expected given the cortical maturation and reduction that has been found during childhood in other studies (Fischer et al., 1997, Munoz et al., 1998). The reason for the discrepancy with other studies may be because the difference between the two age groups of 8-11 years and 13-14 years in the present study was insufficient to show the trend and is smaller than age range of 9-15 years used by Fischer et al. (1997). The reason why preterms still showed a reduction is likely to be partly because of the larger sample size for the longitudinal data. The greater consistency of the effect that was also shown for the cross-sectional data in preterms may be because they showed a more rapid development of antisaccade control during this period than full terms, as reflected by the greater reduction in the antisaccade directional error rate (as illustrated in Figure 8.1).

Although both preterms and full terms showed a significant reduction in the antisaccade error rate, the main aim of this aspect of the research was to determine if the deficit that was found in the antisaccade control in preterms at age 8-11 years, was still present at 13-14 years. Examination of the difference in antisaccade directional error rate between the ages of 8-11 years and 13-14 years revealed that the reduction was far greater in preterms, with a fall of 38.7% compared to 17.8% in full terms. At 13-14 years the antisaccade error rates were subsequently very similar for both preterms (35.5%) and full terms (39.2%) with no statistically significant difference. This implies that although preterms had a deficit at age 8-11 years, the rate of improvement and development was far quicker between 8-11 and 13-14 years than that of full terms, enabling the preterms to 'catch up' and reach a normal level. The original deficit of increased antisaccade directional error rates in preterms age 8-11 years was therefore not a permanent one and may have occurred due to a delay in the development as a direct result of prematurity or due to the recovery of function and development following a lesion in the region of the DLPC.

The other areas of antisaccade control that showed differences between preterms and full terms at age 8-11 years were the proportion of express antisaccade errors which were higher in preterms, the latency of the antisaccades which were shorter and the antisaccade error correction rates which were lower in preterms. At 13-14 years the proportion of express antisaccade errors had reduced in both preterms and full terms and were now similar for both groups. The slight deficit

in the ability to correct antisaccade errors in preterms had disappeared as had the discrepancy in antisaccade latencies. There were no longer any significant differences between preterms and full terms for any of these measures. The reductions in the difference between preterms and full terms in the proportion of express antisaccade errors, latency of antisaccade and antisaccade error correction rate is again likely to be due to an improvement in the development of antisaccade control in preterms as a consequence of greater maturity of the frontal cortex.

10.10ii Development of vergence at age 13-14 years

At 10-11 years preterms had significantly longer vergence latencies than full terms, but other aspects of vergence control were similar for both groups. To assess the development of vergence control, the same group of preterms were retested at 13-14 years. As a result of the study design and recruitment problems, the comparison group of full terms at 13-14 years were different subjects to those originally seen at 10-11 years. This should be taken into consideration when interpreting the results, though variation between different groups of control subjects, recruited with the same inclusion criteria, should be relatively small. The number of subjects for the preterms assessed longitudinally was lower than the full terms assessed cross-sectionally, but analysis using a same subject design has greater statistical power than a cross-sectional design and therefore may be more likely to produce a statistically significant result.

Vergence latency reduced for both preterms (in the region of 70ms) and full terms (in the region of 55ms) between 10-11 years and 13-14 years, but only approached significance for the left eye in preterms. This is likely to be due to the fact that both preterms and full terms had fairly small sample sizes. The time to peak vergence velocity also generally reduced, reaching significance for full terms in the right eye. There were no significant differences in the peak velocity or amplitude of the vergence angle. The reduction in vergence latency in this study between the ages of 10-11 years and 13-14 years compares well with the findings of Yang et al. (2002) where the latency was found to reduce steadily during childhood reaching adult levels by 12 years of age. The actual values for the 'adult level' latencies however, as discussed earlier, were much lower due to methodological differences especially in relation to the target presentation and cue to initiate vergence. As suggested by Yang et al., the reason for the reduction in vergence latency during childhood is likely to be due to the maturation of the frontal cortex. This would therefore explain why the main deficits found in preterms were in the areas of the antisaccade directional error rate and vergence latency, both of which are under the control of areas in the frontal cortex, which matures slowly and could therefore be susceptible to developmental delay as a result of prematurity.

To assess if the improvements in vergence control, particularly latency, had made an impact on the differences between preterms and full terms, both groups were compared at the age of 13-14 years. Unlike the marked improvements that

occurred in antisaccade directional error rates, the vergence latencies made fairly modest improvements over the same time period (in both groups of subjects). Subsequently, at 13-14 years there were still significantly longer vergence latencies (in the region of 70ms longer) in the preterms compared to the full term children. The other aspects of vergence control continued to be similar for both groups at this age. The rate of development of vergence control (in terms of latency) in preterms therefore appears to progress at a slower rate than that of antisaccade control (in terms of the directional error rate). As the subjects tested for vergence were slightly older (10-11 years) than those tested for antisaccades (8-11 years) it would be expected that the extent of improvement may be greater for antisaccades than vergence. However, at 13-14 years the deficit in vergence was still present, unlike antisaccades where there were no longer any significant differences.

10.11 Summary of findings in relation to the third group of hypotheses

At 8-11 years preterms had significantly higher antisaccade directional error rates, lower antisaccade error correction rates and a tendency for a higher proportion of express antisaccade errors and shorter antisaccade error latencies. At the age of 13-14 years there were no longer any significant differences in any area of antisaccade control between preterms and full terms. The hypothesis that preterms show impaired development of eye movement control in the area of antisaccades at the age of 13-14 years is therefore rejected.

For vergence, at the age of 10-11 years preterms had significantly longer vergence latencies than full terms. All other aspects of vergence control were similar for both groups. At 13-14 years the vergence latencies reduced for both preterms and full terms, but the differences between the groups were still significantly different. The hypothesis that preterm children show impaired development of eye movement control in the area of vergence at the age of 13-14 years is therefore accepted.

It would be useful to undertake further research to explore the development of antisaccade and vergence control to increase the number of preterms and especially full terms assessed longitudinally for the control of antisaccades. The number of preterms that were followed however provided a reasonable group in which to study the development and recruiting extra full terms poses less of a disadvantage as there should be less variation between different groups of control subjects. Additionally it would be more beneficial to assess vergence control longitudinally in both full terms and preterms rather than cross-sectionally as was undertaken in this study. It could be argued that assessing another group of preterms at 13-14 years makes comparison difficult as there may be differences introduced due to the fact that they are different subjects rather than as a result of development. This is more problematic for preterms than full term controls due to their greater heterogeneity, but this was minimised to some extent by narrowing the sample examined with the inclusion criteria of IQ>85 and no major neurological abnormalities, which was the same for both groups of

subjects. Additionally, although it was of interest to assess the improvement in control over time within the preterm and full term groups, the main aim was to determine the differences between preterms and full terms which could be achieved by assessing the subjects at different age groups and using different subjects, providing the inclusion criteria remained the same.

10.12 Development of the control of antisaccades and vergence – assessment at 15-16 years

The fourth group of hypotheses stated that preterm children have impaired development of eye movement control in the areas of antisaccades and vergence at 15-16 years of age. Antisaccades will again be addressed first, followed by the development of vergence.

10.12i Development of antisaccades at age 15-16 years

To assess the development of antisaccade control, the data from the 3 age groups tested (8-11, 13-14 and 15-16 years) was compared for both preterms and full terms. The difference in both the directional error rate and error correction rate between the age groups was significant for preterms (8-11 vs. 13-14 and 8-11 vs. 15-16 years) except between the age groups of 13-14 vs. 15-16 years. This may be as a result of a slow down in the rate of development of antisaccade control as the frontal cortex reaches maturity. The latency of the antisaccade also significantly reduced, again as expected due to increased maturity of the frontal cortex, between the ages of 8-11 and 15-16 years. Full terms showed a more steady development of antisaccade control with significant reductions in the

directional error rate between all 3 age groups. At 15-16 years the median error rate for full terms of 14% compared well to other research where the error rate was in the region of 12% at the same age (Munoz et al., 1998). The latencies of both the antisaccades and antisaccade errors in full terms (median 295ms and 208ms, respectively) were similar to the values of 250ms and 150ms respectively, found by Fischer et al. (1997). The reason for the slightly shorter latency found by Fischer et al. is probably because the authors used a gap task (unlike the synchronous task used in the present study) which has been found to reduce latencies in antisaccades by 32±48ms (Klein & Foerster, 2001). Again, unfortunately there is no data on preterms on which to make comparisons.

Full terms in the present study also showed an increase in the antisaccade error correction rate (approaching significance), but only between the ages of 8-11 and 13-14 years. The reason for lack of significant differences between other age groups was because a ceiling effect had occurred by 13-14 years, where the median correction rate had reached 100% and therefore could not improve any further.

At age 15-16 years, comparison of preterms and full terms revealed that preterms made a significantly larger proportion of express antisaccade errors and the median antisaccade directional error rate, though not statistically significant, was notably higher for preterms (24%) than full terms (14%). The difference in error rate is likely to have failed to reach significance due to the very small sample size

and subsequent use of a non-parametric test. This area requires further research to increase the sample size to allow firm conclusions to be drawn. However, the preliminary findings suggest that although preterms made a rapid development in antisaccade control between the ages of 8-11 and 13-14 years, at 15-16 years the development has slowed. At 15-16 years as full terms are reaching adult levels of error rates, preterms appear to have a residual deficit. This may indicate that preterms have a small but permanent deficit in antisaccade control. To investigate this further, it would also be useful to assess preterms up to the age of 20 years of age as the antisaccade error rates in normal subjects have been shown to continue to fall to 10% by 17 years (Munoz et al., 1998) and to 6% in the age range of 18-26 years (Klein & Foerster, 2001).

10.12ii Development of vergence at age 15-16 years

In a similar manner to antisaccades, development of vergence control was assessed by comparing the data in both preterms and full terms at the 3 age groups of 10-11, 13-14 and 15-16 years. The difference in vergence latency (left eye and right eye) between the age groups was significant in preterms except between the ages of 13-14 and 15-16 years. This was the same pattern that was noted for the antisaccade direction error rate and as discussed earlier probably occurred due to a reduction in the rate of development as the frontal cortex reaches maturity. It also highlights the fact that both these areas of oculomotor control have similar periods of development and are affected by the development and maturity of similar cortical regions. The peak vergence velocity in preterms

also reduced throughout the age groups but only approached significance (possibly due to the small sample size) in the right eye between the ages of 10-11 and 13-14 years. The reason for the reduction in velocity is likely to be related to the fact that the amplitude of the vergence angle also reduced between the three age groups, though it did not reach statistical significance. The reason for a reduction in vergence angle over time is not clear and as both the amplitude differences and peak velocity differences were generally not significant, the discrepancies may have occurred by chance and further exploration of this area is required in order to reach a firm conclusion.

The full term group also showed reductions in vergence latency, particularly between the ages of 10-11 and 13-14 years, though statistical significance was not reached between any of the age groups. This is likely to have occurred because, unlike the preterms, the latencies in the full term children were not notably elevated at 10-11 years and therefore the reductions required to reach adult levels were smaller. It is probable that adult level latencies had been reached in the 13-14 year age group, which is comparable to the findings of Yang et al. (2002) where adult levels were reached at 12 years of age. The latencies at all age groups in full terms were much larger than those found by Yang et al. but as discussed previously, the magnitude of the latency is difficult to compare due to important differences in the target and cue to execute vergence. The time to peak velocity also significantly reduced for the right eye between the age of 10-11 and 13-14 years, though reductions were generally evident across all age

groups in both full terms and preterms and is likely to be due to the reductions that occurred in vergence latency.

At 15-16 years vergence latencies were similar for preterms and full terms with no statistically significant differences. This occurred due to the greater reduction in latency in preterms between the age groups of 13-14 and 15-16 years. Preterm children therefore appeared to show developmental delay in vergence control, with full terms reaching adult levels by 13-14 years and preterms reducing the deficit by 15-16 years. As mentioned earlier, the conclusions based on the findings in the 15-16 year age group need to be regarded as provisional due to the small sample size and also absence of longitudinal data. However, the data from the control subjects compares well with other studies and further research with a larger sample will enable firmer conclusions to be drawn.

10.13 Summary of findings in relation to the fourth group of hypotheses

At 15-16 years preterms made a significantly larger proportion of express antisaccade errors and had a tendency to have higher antisaccade directional error rates. The hypothesis that preterms showed impaired development of antisaccade control at 15-16 years is therefore accepted with the acknowledgement that further research is required. The control of vergence showed no significant differences between preterms and full terms on any measure, with the latencies for the preterm group reducing from the age group of 13-14 to 15-16 years to a

similar level to the full terms. The hypothesis that preterms showed impaired development of vergence control at 15-16 years is therefore rejected.

10.14 Visual and binocular function in preterms vs. full terms

Visual and binocular function measurements were collected on preterms and full terms to initially assess if any deficits were present. Following this the visual and binocular function data were analysed together with the reading data to determine if any associations were present and this will be discussed later (10.16).

The distance acuity was significantly better in full terms compared to preterms, though the differences were relatively small and there were no statistically significant differences in near acuity. The overall level of acuity in preterms was the same as that found in other studies (for preterms without ROP) with an overall median of 0.0 LogMAR for distance (O'Connor et al., 2002a). The acuity for near was also similar, but slightly better in the present study (median 0.0 LogMAR), compared to the level of 0.2 found by O'Connor et al. Preterms in both studies had a good level of near acuity though, as 0.2 LogMAR is still better than N5 (equivalent to 0.4 LogMAR), the standard size of newspaper print. To allow comparison with other literature, the proportion of subjects with acuity below normal (worse than 0.0 LogMAR in either eye) was also calculated and compared. The proportion of preterms with below normal acuity in the present study was 36% which was also comparable to the findings (24%) of O'Connor et al. The reason for the higher proportion in the present study is likely to be due to

differences in the classification of abnormal acuity. Whilst both studies used 0.0 LogMAR as the threshold, O'Connor et al. calculated the proportion of preterms with abnormal acuity in relation to the binocular acuity measurements which is likely to have produced a more favourable outcome than the method used in the present study. The proportion of preterms with abnormal acuity found in this study is also higher than the level of 6.5% found by Cooke et al. (2004). However, the discrepancy is likely to be explained by the fact that Cooke et al. used the Snellen test which is less likely to detect abnormal acuity and the authors also used a higher threshold of 6/9 (6/9.5 is equivalent to 0.2 LogMAR) for classifying abnormal acuity. Whilst a relatively high proportion of preterms in the present study were classed as having acuity below normal, in most cases the level of acuity was only a few letters below normal in one eye and though the level of distance acuity was significantly better in full terms, the median distance and near acuities in the preterm group were still at a normal level.

With respect to ocular alignment, there were no cases of manifest strabismus found in the sample of preterms (or full terms) in this study. This is in contrast to the reports by Cooke et al. (2004) of 13.6% of preterms with strabismus and 19.3% by O'Connor et al. (2002b). The discrepancy is likely to be due to the fact that the preterm sample in the present study was a low risk group due to the selection criteria requiring the preterms to be free from major neurological deficits, with IQ greater than 85 and a uniocular acuity of no worse than 0.5 LogMAR. Absence of strabismus also provides further evidence that in this

group of preterms there were no significant deficits at the level of the brainstem. Differences were also present between the prevalence of strabismus in the full term group in the present study and the levels found by Cooke et al, (1.4%) and O'Connor et al. (3%). This is likely to have arisen because the prevalence in full terms is generally quite low and in the present study some cases of strabismus (with amblyopia) would have been excluded from the full term group due to the exclusion criteria relating to the minimum uniocular acuity. Preterms did show some evidence of misalignment however, as the proportion of subjects with latent strabismus was significantly higher in preterms (39%) compared to full terms (15%). This also explains the higher prism cover test measurements in preterms for near (approaching significance, $p=0.07$), with most cases of latent strabismus being of the convergence weakness exophoria type.

All other visual and binocular measures did not show any significant differences between the preterm and full term children. The reason why the level of stereopsis was not significantly different between the two groups, unlike that found by others (Cooke et al., 2004, Hard et al., 2000), is likely to be because there were no cases of manifest strabismus or subjects with severely impaired acuity in the preterm cohort in the present study. Despite the fact that a greater proportion of preterms had latent strabismus and a larger near angle of deviation than full terms, the prism fusion range assessed by both blur and break point was also similar for both groups. This indicates that the latent strabismus in preterms was equally well controlled compared to the full terms. The values of the prism

fusion range in this study were in the region of 35^{Δ} (blur) and 44^{Δ} (break) for both preterms and full terms, which is slightly lower than the values of 45^{Δ} (blur) and 59^{Δ} (break) reported by Melville & Firth (2002). The subjects used by Melville and Firth however, were orthoptic students who had experience of the test and therefore discrepancies may have occurred due to a practice effect. There were also notable differences between the studies with respect to the age of the subjects used.

A variety of accommodative measures was also undertaken on preterms (and full terms) to assess the presence of any deficits; this does not appear to have been investigated in other studies. Research assessing the refractive status and aetiology of myopia in preterms has identified that (in addition to other factors) the degree of myopia is related to the thickness of the lens (Choi et al., 2000). Given that the thickness of the lens changes during accommodation (Garner & Yap, 1997), it is possible that alteration in lens thickness could affect the biomechanics of accommodation resulting in impairment of accommodation either in the amplitude or in the ability to exert and relax accommodation (facility). However, despite this potential risk, the preterm group showed no significant differences on any measure of accommodation in relation to full terms. The mean value of monocular accommodative facility (5.6±2.7 cycles per minute) and binocular accommodative facility (5.2±2.6 cycles per minute) in full terms compared well (7.2±3.6 monocular, 4.3±2.7 binocular; cycles per minute) with other children of a similar age (Jimenez et al., 2003). The values for the near point of accommodation in full terms (converted from cm to dioptres to allow

comparison with other research) were also comparable (full terms: binocular 16.7D, median) to the expected value of 15.2D for this age group, using Hofstetter's formula (Hofstetter, 1950) and to other research where a value of 14.4D was reported (Sterner et al., 2004). Sterner et al. however, found lower values than expected for monocular accommodative amplitude based on Hofstetter's formula. The levels were also low compared to the present study. Values for the amplitude of accommodation in the present study were much smaller when using the minus lens method in comparison to the method using the RAF rule, sometimes referred to as the push-up method. This is not uncommon however, as the push-up method is thought to significantly overestimate the true amplitude of accommodation (Rosenfield & Cohen, 1996) and discrepancies of over 3D have been shown between the 2 methods in adults (Ostrin & Glasser, 2004). The discrepancy was also greater for younger adults with more active accommodation and may therefore be even larger in children.

The visual and binocular function of the preterm group was therefore very similar to that of full terms with differences only present for distance acuity, where preterms still had an overall group median in the normal range and a greater proportion of preterms had latent strabismus, but all cases were well controlled.

10.15 Reading ability in preterms

As a group, preterms had significantly poorer reading ability than full terms when tested for reading accuracy and comprehension (Neale Test) and also when

using single words to give an overall reading score (Graded Word Test). Despite the differences with the controls, the preterm group still had mean scores well within normal limits on all reading measures (98.1, 98.3, 97.5 and 106.8). The reduced mean reading scores for the preterm group may partly be due to their slightly reduced IQ scores as the reading scores and IQ were significantly correlated for the Graded Word Test and the comprehension element of the Neale Test. The accuracy and rate elements of the Neale Test however were not significantly correlated with the IQ. The latter two reading areas are more likely to reflect problems affecting reading ability other than IQ, as they require fluent reading of a passage. Conversely, the Graded Word Test only assesses reading on the basis of one word at a time which gradually increases in severity, and like the comprehension aspect of the Neale, is more likely to be related to IQ.

The range of reading scores was greater for preterms with notably lower minimum values (PT: 70, 79, 76 and 87; FT: 80, 89, 89 and 92) indicating the presence of specific reading difficulties within the preterm group. This is similar to other studies (Bowen et al., 2002, Saigal et al., 2000), where for example a mean standardised reading score of 94.8 was achieved by the preterm group, which was significantly lower than the 103.5 achieved by full terms, with a large range in the preterm group of 51-124 (Bowen et al., 2002). The range of reading scores contained a lower minimum than that found in the present study which is likely to be because of the inclusion criteria that was used.

The proportion of preterms with specific reading difficulties (SRD) was significantly greater in preterms (33%) than full terms (3%). This is slightly larger than other reports of 28% (Saigal et al., 1992) and 23% (Grunau et al., 2002), but both of these studies used different criteria (extremely low birth weight) to recruit preterm children than the present study, which may have resulted in their subjects having greater overall impairments and therefore less likely to be classified as having specific learning difficulties. Comparison between the studies is also difficult as different reading assessments were used. Nevertheless, the findings of the present study are in general agreement with both Saigal et al. and Grunau et al. that preterms are at risk from reading difficulties that cannot simply be attributed to an overall cognitive deficit and reduction in IQ. This was supported by comparison of the reading scores and IQ, which for preterms with SRD did not show any significant correlations on any of the reading measures. It could be argued that the criteria used in the present study to define SRD, of a score of less than 85 on any one of the reading tests, may have overestimated the true level of reading problems. However, 58% of preterms classified as having SRD, had reading scores below 85 on 2 or more of the reading assessments. Also there is no clear argument for stipulating that, for SRD classification, a score of below 85 must be achieved in more than one reading measure. The fact that some preterms had a reduced score in only one area indicated that these children still had reading difficulties, but only in a specific area of reading ability (accuracy, comprehension or reading speed).

The reading ability was therefore clearly reduced in preterms compared to full terms though as a group the scores were within normal limits. Additionally there were a substantial proportion of preterms identified with SRD and the following sections will assess if there is evidence for an association between the visual, binocular function and oculomotor control with the reading difficulties and thus address the final group of hypotheses.

10.16 The association between visual and binocular function and oculomotor control with reading difficulties in preterms

In order to assess if reading difficulties were associated with the visual, binocular function and oculomotor performance, given the relatively small number of subjects and subsequent difficulties in satisfactorily identifying correlations, a binary analysis was used. It would be useful to recruit further subjects to allow the use of regression analysis to determine if the visual, binocular function or oculomotor performance could accurately predict reading ability in preterms.

10.16i The association between visual and binocular function with reading difficulties in preterms

There were no significant differences in the measures of acuity, near point of convergence, fusion range, stereopsis, accommodation or size of heterophoria between preterms with and without reading difficulties. The interquartile range showed slightly poorer levels of stereopsis and the near prism cover test measurements were slightly higher in preterms with SRD. This may have been due to a greater proportion of preterms with SRD having latent strabismus (50%)

compared to those without SRD (33%), though the difference was not significant. Large latent strabismus at near has been shown to have a negative effect on reading ability (Rundstrom & Eperjesi, 1995). However, the latent strabismus in the preterms in the present study is unlikely to have caused reading difficulties as the size of deviation was modest, the control was very good in all cases, and there were no significant differences in the fusion range between preterm and full term children. None of the visual and binocular function measures therefore appear to be associated with the reading difficulties experienced by the preterm children in this study. This was not really surprising given that preterms showed very similar performances to the full term children in the majority of assessments.

10.16ii The association between oculomotor control and reading difficulties in preterms

Comparison of saccade control in preterms with and without SRD showed that preterms with SRD had a significantly larger saccade gain (for rightward saccades only). Saccade dysmetria has been shown to cause reading problems in other conditions such as Friedreich's ataxia (Ciuffreda et al., 1985) and Huntington's chorea (Pirozzolo & Rayner, 1979), though the deficits in saccadic control in these conditions were far more severe than those found in the preterms with SRD. It is unlikely therefore that the dysmetria found in the preterms with SRD would be the sole cause of their reading difficulties and it is unclear why only rightward saccades showed significantly larger gains. It remains a possibility that the saccade gain could be associated with the reading difficulties

in preterms and further research with a larger sample, if possible with preterms experiencing varying degrees of reading difficulty, would allow a firmer conclusion to be drawn. It would also be useful to assess saccades using a gap paradigm and more thoroughly investigate the presence of express saccades, which have been reported to occur more frequently in dyslexics (Biscaldi et al., 1994, Fischer & Weber, 1990). Dyslexics are clearly a distinct group from the preterms who suffer with specific reading difficulties, but it may be useful to draw some comparisons given that both groups have reading difficulties in the presence of normal IQ and the association between various eye movement abnormalities and reading difficulties has been explored in dyslexia (Biscaldi et al., 2000, Eden et al., 1994, Fischer & Weber, 1990, Stein, 2001). There were no other significant differences in saccadic control between preterms with and without SRD.

The pursuit data was also very similar for both preterms with and without reading difficulties and though preterms with SRD had very slightly shorter latencies and very slightly lower peak slow eye velocities, the differences were not significant. It could be expected that pursuit deficits would be associated with reading difficulties given the magnocellular theory of dyslexia (Stein, 2001), as discussed in Chapter 4 (section 4.6). Also preterms have been found to perform poorly on a motion processing task which indicated preterms may be at risk of magnocellular deficits (Downie et al., 2003). However, the magnocellular deficits found by Downie et al. were not correlated with the reading ability of the preterm children.

Also there is a large amount of controversy surrounding the magnocellular theory of dyslexia (Ramus, 2003) with several studies providing evidence contrary to the theory (Amitay et al., 2002, Chiappe et al., 2002, Ramus et al., 2003). Given the fact that magnocellular deficits may not be linked to reading problems and although evident in some preterms were also not associated with their reading ability, it does not appear likely that the control of smooth pursuit would be predictive of reading difficulties and therefore explains the lack of any difference in pursuit performance between preterms with and without SRD in the present study.

Analysis of the antisaccade data revealed that whilst the directional error rates were significantly higher in preterms than full terms, there was no significant difference between preterms with and without SRD and in fact the error rates were slightly higher in preterms without SRD. This is contrary to the findings in dyslexia where significantly higher error rates were found in dyslexic children (62% at age 11 years) compared to controls (45%) of the same age (Biscaldi et al., 2000). The reason for the discrepancy may be because the aetiology of the reading disorder in dyslexia is likely to be vastly different to that of preterms. Of interest however, is the fact that the percentage of dyslexics with significantly higher error rates rose dramatically between the ages of 13 and 17 years and this would not have been detected in the present study (the reading data was only collected on preterms up to the age of 12 years: Groups 1 and 2). It may be useful therefore to assess the reading ability of preterms up to the age of 17 years and

make comparisons between their reading ability and antisaccade performance, in particular the directional error rates.

There were also no significant differences between preterms with and without SRD with respect to the antisaccade error correction rate or latency of the antisaccade error. This is again contrary to the findings of Biscaldi et al. (2000) where the correction rate was significantly lower in dyslexics than controls, particularly between 13 and 17 years of age. There were some significant differences however in the present study between preterms with and without SRD. Preterms with SRD had significantly shorter antisaccade latencies and made significantly more express antisaccade errors. This is suggestive of a difficulty with the inhibition of saccades and it is surprising therefore preterms with SRD did not have higher directional error rates. Although the error rates did not differentiate between preterms with and without SRD they were still substantially higher than those found in full terms (PT with SRD 69.3% vs. FT 54.2%). The reason for the differences relating to antisaccade initiation but not directional error rate may be because preterms with SRD suffered from an additional lesion affecting the caudate nucleus (Abernethy et al., 2004, Abernethy et al., 2002, de Vries et al., 1997, Nosarti et al., 2005, Reeder et al., 1982). A lesion of the caudate nucleus may be expected to cause difficulties in the generation of a saccade rather than unwanted or express saccades due to its role in inhibiting the SNpr, which in turn inhibits the superior colliculus. A caudate lesion which prevented or reduced the inhibition of the SNpr would

allow the SNpr to continue to inhibit the superior colliculus and therefore prevent the generation of a saccade. However, the caudate has been found to both stimulate as well as inhibit SNpr neurones, via an indirect pathway through the subthalamic nucleus (Hikosaka et al., 1993). The caudate nucleus therefore also appears to have a role in facilitating the SNpr neurones, thus inhibiting the generation of saccades, and it follows that a lesion of the caudate could disrupt the control of fixation and saccade initiation and lead to express saccades generated by the superior colliculus. A caudate lesion, if leading to an impaired ability to suppress saccades, may also be expected to lead to increased antisaccade directional error rates in addition to a higher proportion of express saccades. Both of these behaviours were noted in so called 'express saccade makers' by Biscaldi et al. (1996). However, in the preterm children with SRD the error rates are already raised relative to full terms and perhaps a ceiling effect has been reached. Even in the youngest age group of normal children tested, where error rates are at their highest, the rates have only been found to be in the region of 50% at 5-8 years (Munoz et al., 1998), 52.5% at 6-7 years (Klein & Foerster, 2001), 57.6% at 7 years (Fukushima et al., 2000) or slightly higher in one study at 65% at 8-10 years (Fischer et al., 1997). Although preterms with SRD had a higher proportion of express antisaccade errors, the proportion of express saccades on the standard prosaccade task was similar for both groups of preterms and did not differentiate between them in terms of reading difficulties. The interquartile ranges were higher though in preterms with SRD and it would be

useful to investigate this area further with more subjects and additionally with the use of a gap paradigm, which would more readily generate express saccades.

In a similar manner to the antisaccades, the vergence latencies though significantly longer in preterms compared to full terms were not significantly different between preterms with and without SRD. Given that an area in the prearcuate cortex, anterior to the saccade relation region of the FEF has been found to contain neurones responsible for vergence (Gamlin & Yoon, 2000), this provides further evidence that deficits in the region of the frontal cortex do not differ in severity between preterms with and without SRD. An aspect of vergence control that has been reported to lead to reading difficulties in other subjects is convergence insufficiency, with a reduced near point of convergence (Ciuffreda & Tannen, 1995, Rundstrom & Eperjesi, 1995). The amplitude of vergence measured in both preterms with and without SRD however, showed no differences and therefore does not appear to be related to the reading difficulties. The peak vergence velocities and time to peak velocity were also not significantly different between both groups of preterms. Despite the differences found between preterms and full terms in vergence control with significantly longer vergence latencies, the requirement of vergence in the reading process at the usual reading distance and the involvement of vergence during reading to reduce fixation disparity (Liversedge et al., 2006), the control of vergence does not appear to be associated with the reading difficulties experienced by the preterm subjects.

The binocular co-ordination of saccades is also important during reading (Liversedge et al., 2006), especially given that the eyes tend to be divergent before and during a saccade followed by a convergent dynamic overshoot and post-saccadic convergent drift (Collewijn et al., 1988, Kapoula et al., 1986). It would seem possible therefore that disruption in the binocular co-ordination of the eyes could cause reading difficulties and perhaps lead to jumbling of the letters (Stein et al., 2000). However, the amplitude of disconjugacy in preterms with SRD did not show any consistent differences to those without SRD. Likewise the amount of post-saccadic drift was also similar for both groups of preterms. Whilst impairment of the binocular co-ordination of saccades may be an area that would be expected to cause reading difficulties, there were no significant differences in this area between preterm and full term children. Additionally, the binocular control found in preterms in other areas was perfectly adequate with normal fusion ranges, levels of stereopsis and absence of manifest strabismus. An absence of differences in the binocular co-ordination of saccades between preterms with and without SRD probably reflects the fact the preterms in this study were generally free from all anomalies of binocular function (though preterms had a greater proportion of subjects with latent strabismus all were well controlled), which is likely to be due to their low risk status as discussed previously.

The final aspect of oculomotor control that was compared in preterms with and without SRD was fixation. The most frequent saccadic intrusion in both preterms

and full terms was the SWJ. The rate per minute of SWJ's in preterms with SRD was almost double that of preterms without SRD and approached significance. Additionally the peak velocity of the SWJ was significantly higher in preterms with SRD. Surprisingly the rate per minute of 'other saccadic' intrusions was significantly higher in preterms without SRD but the rates for both groups were small (with SRD 0.7, without SRD 1.5) and the difference in rate of 0.8 per minute is not likely to be of clinical importance. A higher rate of SWJ and increased peak velocity in preterms with SRD could be related to the increased proportion of express antisaccade errors both of which indicate a potential disorder of fixation control. However, whilst the rate of SWJ was substantially higher in preterms with SRD and higher than the full term controls, it is also very similar to the level found in normal, albeit adult subjects (Abadi & Gowen, 2004). As the rate of SWJ's in preterms with SRD is similar to the level found in normal adult subjects this is not likely to have contributed to the reading difficulties. Preterms with SRD though did have SWJ's with an increased peak velocity that was not as a result of larger SWJ amplitudes which were very similar for both groups of preterms and may therefore indicate a disturbance to the main sequence relationship. This is an area which needs to be investigated with a larger sample to enable comparison of the main sequence relationships between preterms with and without SRD. The combination of an increased SWJ rate, increased SWJ peak velocities and larger proportion of express antisaccade errors in preterms with SRD may therefore be associated with the reading difficulties in preterms and could indicate a mild deficit in the control of fixation.

10.17 Summary of findings in relation to the fifth group of hypotheses

Though preterms had a significantly higher proportion of latent strabismus and poorer distance acuity than full terms, both of these findings were of a mild nature. The latent strabismus was well controlled and the acuity was still at an overall normal level. All other measures of visual and binocular function were similar in preterms and full terms and it is not surprising therefore that none of these measures were statistically different between preterms with and without SRD. Based on these initial findings, the hypothesis that the visual acuity, latent strabismus, stereopsis, near point of accommodation, accommodative amplitude, accommodative facility, near point of convergence or fusional reserves are associated with reading difficulties in preterms is therefore rejected. It is accepted however that the rejection of the hypothesis must remain tentative and that a larger sample of preterms with SRD would allow a more robust conclusion to be drawn.

In terms of oculomotor control there were some significant differences between preterms with and without SRD in a variety of oculomotor behaviours. Saccade gain was larger in preterms with SRD but only for rightward saccades but the control of smooth pursuit showed no significant differences. In antisaccades, preterms with SRD had shorter antisaccade latencies and made more express antisaccade errors. The control of vergence and binocular co-ordination of saccades despite having an important role in the reading process did not differentiate between preterms with and without SRD. Finally, the control of

fixation revealed that preterms with SRD had a higher rate and peak velocity of SWJ's, which perhaps in addition to the increased proportion of express antisaccade errors could indicate a mild deficit of fixation control in preterms with SRD. Whilst the oculomotor deficits in preterms with SRD may be associated with their reading difficulties, it appears unlikely that due to the lack of severity, they would be the cause of the reading difficulties experienced by preterms. The hypothesis that the control of saccades, antisaccades and fixation may be associated with reading difficulties in preterms is therefore accepted, whilst the hypothesis that the binocular co-ordination of saccades and control of smooth pursuit and vergence may be associated with reading difficulties in preterms is rejected.

10.18 Summary and implications of the main findings from the research

Preterms in this study were a relatively low risk group with IQ of greater than 85 and were free from major neurological abnormalities. It should be noted that those with multiple disabilities and severe neurological abnormalities only account for 14% of preterms (Whitfield et al., 1997) and this sample is therefore likely to be representative of a large proportion of preterm children. Given the variety of cerebral lesions that are known to affect preterms it was surprising, though encouraging to discover that the control of saccades, their binocular co-ordination and control of fixation generally showed no significant differences in relation to full terms. In smooth pursuit, preterms showed a tendency to have slightly longer latencies, possibly indicative of a mild cortical deficit affecting

the normal maturation process, though a larger sample size and additional use of a predictive target would be required in order to make a firm conclusion about the status of smooth pursuit control. The control of antisaccades and vergence revealed the greatest amount of impairment in preterms with increased directional error rates, shorter antisaccade latencies, a larger proportion of express antisaccade errors and longer vergence latencies. By 13-14 years however, all antisaccade deficits in preterms appeared to have resolved, though the deficit affecting vergence latency still remained. At 15-16 years, the improvement in antisaccade control did not appear to be sustained. Preterms again made significantly more express antisaccade errors and (though not reaching statistical significance) had a higher directional error rate. The number of preterms and full terms tested at this age was low and therefore conclusions must be tentative, but these initial results may indicate a permanent residual deficit of antisaccade control in preterms. The control of vergence however was now similar for both groups. The visual and binocular functions in preterms were similar to full terms in contrast to other reports (Cooke et al., 2004, O'Connor et al., 2002a), but the exclusion criteria in terms of IQ, major neurological abnormalities and acuity are likely to account for the discrepancies.

The implications of the oculomotor findings are therefore that preterms may have a subtle deficit in the frontal cortex or disrupted maturation indicated by the impairments of antisaccade control and vergence initiation. The antisaccade error rates may be associated with and help to predict other behavioural problems such

as ADHD and disorders of executive function which have been reported in preterms (Botting et al., 1997, Salt & Redshaw, 2006). These findings also support the possibility of a deficit in the frontal cortex. Yet based on the initial findings of this study, parents of preterm children who are free from neurological abnormalities, can be reassured that for the preterm group as a whole, the control and subsequent development of saccades and fixation appear to be normal. Further research with a larger sample will allow the proportion of preterms with oculomotor deficits to be more clearly identified to assess if this is greater than that of controls. It would also be useful to perform MR imaging on preterm children and compare cerebral volumes of structures involved in the oculomotor pathways in preterms with and without oculomotor deficits.

In line with other research (Grunau et al., 2002, Saigal et al., 1992) specific reading difficulties were present in a substantial proportion of preterms. Preterms with reading difficulties had larger saccade gain for rightward saccades, a higher proportion of express antisaccade errors, shorter latency of antisaccades and a higher frequency and velocity of square wave jerks than preterms without reading difficulties. Another implication of the oculomotor findings therefore, is that although the deficits were unlikely to be the cause of the reading difficulties in preterms, they could be associated with the reading problems. Further research involving more subjects will help to determine if the deficits of oculomotor control could predict reading difficulties in preterm children.

If the oculomotor impairments were found to be predictive of executive dysfunction and reading difficulties, the simple oculomotor tasks used in this study would be a useful assessment that could help with the early identification of these behavioural issues and which may assist with the early implementation of intervention or treatment programmes. This is an area that needs to be explored in the future.

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Appendix 1 Published output and abstracts

Papers published:

Newsham D, Knox PC. (2001). A review of reading difficulties in relation to saccadic and visual anomalies in very low birth weight children. *British Orthoptic Journal, 58,* 12-19.

Newsham, D., & Knox, P.C. (2002). Oculomotor control in a group of very low birth weight (VLBW) children. *Prog Brain Res, 140,* 483-498.

Newsham D, Knox PC and Cooke RWI. (2004). Binocular co-ordination of saccades in children born preterm. *Trans 10th International Orthoptic Congress,* pp. 187704024x (CD-ROM)

Abstracts:

Newsham, D., & Knox, P.C. (2002). Oculomotor Control - A Problem for Lightweights? *Invest. Ophthalmol. Vis. Sci., 43* (12), 958-.

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Newsham, D., Knox, P.C., & Cooke, R.W.I. (2004). Increased vergence latency provides further evidence of a frontal lobe deficit in children born preterm. *Invest. Ophthalmol. Vis. Sci., 45* (5), 3428-.

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Appendix 2.1 Normality of the distribution of the demographical data

Demographical Data	Kolmogorov-Smirnov Statistic Z and (p value)			
	Saccades and Smooth Pursuit		Antisaccades	
	Preterm	Full term	Preterm	Full term
Age when tested	0.588 (p=0.9)	0.739 (p=0.6)	0.478 (p=1.0)	0.600 (p=0.9)
Full scale IQ	0.594 (p=0.9)	0.632 (p=0.8)	0.623 (p=0.8)	0.557 (p=0.9)
GA	1.025 (p=0.2)	N/A	1.290 (p=0.07)	N/A
Birth weight	0.552 (p=0.9)	N/A	0.634 (p=0.8)	N/A

Appendix 2.2 Normality of the distribution of the saccade data

Saccade Measurement	Kolmogorov-Smirnov Statistic Z and (p value)	
	Preterm	Full term
Gain leftward	0.803 (0.5)	0.672 (0.8)
Gain rightward	0.744 (0.5)	0.440 (1.0)
Latency leftward	0.949 (0.3)	0.510 (1.0)
Latency rightward	0.620 (0.8)	0.451 (1.0)
Peak velocity leftward	0.606 (0.9)	0.390 (1.0)
Peak velocity rightward	0.382 (1.0)	0.577 (0.9)
Duration leftward	0.733 (0.7)	0.471 (1.0)
Duration rightward	0.527 (0.9)	0.478 (1.0)
Proportion of express saccades leftward	1.572 (0.01)	1.106 (0.2)
Proportion of express saccades rightward	1.444 (0.03)	1.209 (0.1)

Appendix 2.3 Normality of the distribution of the smooth pursuit data

Smooth pursuit measurement	Kolmogorov-Smimov Statistic Z and (p value)	
	Preterm	Full term
Latency leftward	0.605 (0.9)	0.365 (1.0)
Latency rightward	0.570 (0.9)	0.537 (0.9)
Acceleration leftward	1.211 (0.1)	0.686 (0.7)
Acceleration rightward	0.805 (0.5)	0.655 (0.8)
Velocity (0-20ms) leftward	0.964 (0.3)	0.549 (0.9)
Velocity (0-20ms) rightward	0.732 (0.7)	0.630 (0.8)
Velocity (80-100ms) leftward	0.610 (0.9)	0.696 (0.7)
Velocity (80-100ms) rightward	0.761 (0.6)	0.928 (0.4)
Velocity (open loop) leftward	0.537 (0.9)	0.759 (0.6)
Velocity (open loop) rightward	0.488 (1.0)	0.612 (0.8)
Peak slow eye velocity leftward	0.432 (1.0)	0.678 (0.7)
Peak slow eye velocity rightward	0.660 (0.8)	0.540 (0.9)

Appendix 2.4 Normality of the distribution of the antisaccade data

Antisaccade measurement	Kolmogorov-Smirnov Stat Z and (p value)	
	Preterm	Full term
Directional error rate	0.513 (1.0)	0.562 (0.9)
Rejection rate	0.843 (0.5)	0.817 (0.5)
Latency of antisaccade errors	0.448 (1.0)	0.623 (0.8)
Percentage of express saccades	0.982 (0.3)	1.155 (0.1)
Antisaccade error correction rate	0.713 (0.7)	1.253 (0.09)
Antisaccade latency	0.389 (1.0)	0.988 (0.3)

Appendix 2.5 Normality of the distribution of the demographical data for children recruited for Experiment 2

Demographical Data	Kolmogorov-Smirnov Statistic Z and (p value)	
	Preterms	Full terms
Age when tested	0.756 (p=0.6)	0.565 (p=0.9)
Full scale IQ	0.544 (p=0.9)	0.564 (p=0.9)
GA	0.835 (p=0.5)	N/A
Birth weight	0.585 (p=0.9)	N/A

Appendix 2.6 Normality of the distribution of the binocular saccade measurements, K-S stat = Kolmogorov-Smirnov test statistic Z, L=leftward saccades, R=rightward saccades

Measurement of eye movement	K-S Stat Z (p value)	
	Preterm	Full term
Amplitude of (L) saccadic disconjugacy (convergent)	0.617 (0.8)	0.527 (0.9)
Amplitude of (L) saccadic disconjugacy (divergent)	1.061 (0.2)	0.761 (0.6)
Amplitude of (R) saccadic disconjugacy (convergent)	0.541 (0.9)	0.539 (0.9)
Amplitude of (R) saccadic disconjugacy (divergent)	0.845 (0.5)	0.679 (0.7)
Percentage of divergence of (L) saccadic disconjugacy	0.963 (0.3)	0.824 (0.5)
Percentage of divergence of (R) saccadic disconjugacy	1.072 (0.2)	0.798 (0.5)
Post-saccadic drift (L) at 75ms (convergent)	0.709 (0.7)	0.620 (0.8)
Post-saccadic drift (L) at 75ms (divergent)	0.555 (0.9)	0.714 (0.7)
Post-saccadic drift (R) at 75ms (convergent)	0.539 (0.9)	0.511 1.0
Post-saccadic drift (R) at 75ms (divergent)	0.488 (1.0)	0.402 (1.0)
Post-saccadic drift (L) at 150ms (convergent)	0.624 (0.8)	0.377 (1.0)
Post-saccadic drift (L) at 150ms (divergent)	0.695 (0.7)	0.404 (1.0)
Post-saccadic drift (R) at 150ms (convergent)	0.507 (1.0)	0.625 (0.8)
Post-saccadic drift (R) at 150ms (divergent)	0.641 (0.8)	0.465 (1.0)
Percentage of divergence (L) of post-saccadic drift at 75ms	0.787 (0.6)	0.653 (0.8)
Percentage of divergence (R) of post-saccadic drift at 75ms	0.764 (0.6)	0.718 (0.7)
Percentage of divergence (L) of post-saccadic drift at 150ms	0.670 (0.8)	0.749 (0.6)
Percentage of divergence (R) of post-saccadic drift at 150ms	0.692 (0.7)	0.675 (0.8)

Appendix 2.7 Normality of the distribution of the vergence measurements

Vergence measurement	Kolmogorov-Smirnov Statistic Z and (p value)	
	Preterm	Full term
Vergence latency left eye	0.674 (0.8)	0.493 (1.0)
Vergence latency right eye	0.605 (0.9)	0.502 (1.0)
Vergence peak velocity left eye	0.581 (0.9)	0.604 (0.9)
Vergence peak velocity right eye	0.370 (1.0)	0.375 (1.0)
Time to peak velocity left eye	0.637 (0.8)	0.633 (0.8)
Time to peak velocity right eye	0.652 (0.8)	0.616 (0.8)
Amplitude of vergence angle	0.768 (0.6)	0.611 (0.9)

Appendix 2.8 Normality of the distribution of the fixation measurements

Fixation measurement	Kolmogorov-Smirnov Statistic Z and (p value)	
	Preterm	Full term
Square wave jerk rate per min	0.552 (0.9)	0.551 (0.9)
Square wave jerk amplitude	1.162 (0.1)	0.992 (0.3)
Square wave jerk peak velocity	0.990 (0.3)	0.817 (0.5)
Square wave jerk duration	0.948 (0.3)	0.795 (0.6)
Other SI rate per min	1.182 (0.1)	0.886 (0.4)
Other SI amplitude	0.992 (0.3)	0.500 (1.0)
Other SI peak velocity	0.841 (0.5)	0.597 (0.9)
Other SI duration	0.593 (0.9)	0.748 (0.6)
All SI combined rate per min	0.499 (1.0)	0.458 (1.0)
All SI combined amplitude	1.263 (0.08)	0.699 (0.7)
All SI combined peak velocity	0.918 (0.4)	0.398 (1.0)
All SI combined duration	0.794 (0.6)	0.656 (0.8)

Appendix 2.9 Normality of the distribution of the reading data and IQ in preterms and full terms, K-S stat = Kolmogorov-Smirnov test statistic

Measure of reading ability	K-S Stat Z (p value)	
	Preterm	Full term
The Graded Word Reading Test	0.596 (0.9)	0.528 (0.9)
Reading accuracy (Neale Analysis of Reading Ability – Revised)	0.769 (0.6)	0.689 (0.7)
Reading comprehension (Neale Analysis of Reading Ability – Revised)	0.874 (0.4)	0.877 (0.4)
Reading rate (Neale Analysis of Reading Ability – Revised)	0.536 (0.9)	1.119 (0.2)
IQ score	0.623 (0.8)	0.557 (0.9)

Appendix 2.10 Normality of the distribution of the visual and binocular function data in preterms and full terms, K-S stat = Kolmogorov-Smirnov test statistic

Visual and binocular function assessment	K-S Stat Z (p value)	
	Preterm	Full term
Near acuity left eye (LogMAR)	1.821 (0.003)	1.939 (0.001)
Near acuity right eye (LogMAR)	2.190 (0.001)	1.629 (0.01)
Distance acuity left eye (LogMAR)	2.203 (0.001)	1.089 (0.2)
Distance acuity right eye (LogMAR)	2.334 (0.001)	1.327 (0.06)
Near point of convergence	2.661 (0.001)	3.052 (0.001)
Stereopsis (TNO)	2.588 (0.001)	1.822 (0.003)
Near point of accommodation left eye (RAF rule)	1.734 (0.005)	2.104 (0.001)
Near point of accommodation right eye (RAF rule)	1.691 (0.007)	2.265 (0.001)
Near point of accommodation binocularly (RAF rule)	1.777 (0.004)	2.071 (0.001)
Prism fusion range (blur point) near	0.750 (0.6)	0.591 (0.9)
Prism fusion range (break point) near	0.638 (0.8)	1.049 (0.2)
Prism fusion range (blur point) distance	0.818 (0.5)	1.100 (0.2)
Prism fusion range (break point) distance	0.567 (0.9)	0.935 (0.4)
Prism cover test near	2.126 (0.001)	2.811 (0.001)
Prism cover test distance	2.667 (0.001)	2.857 (0.001)
Amplitude of accommodation left eye	0.564 (0.9)	0.910 (0.4)
Amplitude of accommodation right eye	0.724 (0.7)	1.047 (0.2)
Accommodative facility left eye	0.708 (0.7)	0.974 (0.3)
Accommodative facility right eye	0.978 (0.3)	0.886 (0.4)
Accommodative facility binocularly	0.773 (0.6)	1.146 (0.2)