Cerebral Visual Impairment in Children Born Prematurely

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Author's declaration

'I declare that, except where explicit reference is made to the contribution of others, that this dissertation is the result of my own work and has not been submitted for another degree at the University of Glasgow'.

Signature _____

Abstract

Cerebral visual impairment (CVI) is the commonest cause of impaired vision in childhood. Prematurely born children are at significant risk of damage to the brain with outcomes including cerebral palsy and low IQ.

This study presents the results of an investigation of multiple aspects of visual function in a cohort of 46 prematurely born children (<37 weeks) aged 5.5 years -12.3 years and attending mainstream education, compared with an age-matched cohort of 130 term-born children.

Fifteen of the 46 (33%) prematurely born children revealed behaviours corresponding to CVI on cluster analysis of a CVI questionnaire, a screening tool used to aid structured clinical history taking. In these children, abnormalities of stereoacuity, contrast sensitivity and eye movements were more frequent and in addition they were born 1½ weeks earlier and around 300g lighter on average than their unaffected peers. These children also performed worse than controls on all visual attention and perception tests except visual closure, while the remaining 31 prematurely born children performed no differently to controls.

This study highlights the incidence of prematurely born children with manifest CVI related difficulties. No visual perception test or routine ophthalmic test picked out those children identified with difficulties by the CVI questionnaire. The CVI questionnaire could be an effective means of identifying children at risk of CVI.

Associated presentations and publications

Journal articles

Catriona Macintyre-Béon, Richard Bowman, David Young, Gordon Dutton, Kate Mitchell, Judith Simpson, Gunter Loffler, Ruth Hamilton, 2013. Cerebral visual dysfunction in prematurely born children in mainstream school. *Documenta Ophthalmologica, 127, pp 89-102*.

Catriona Macintyre-Béon, David Young, Julie Calvert, Hussein Ibrahim, Gordon Dutton, and Richard Bowman, 2012. Reliability of a question inventory for structured history taking in children with cerebral visual impairment. *EYE, 26 (10), pp 166-176.*

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Chapter in book

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Poster presentations

Catriona Macintyre-Béon, Kate Mitchell, Elizabeth McDonald, Gordon Dutton. 'We see it differently' Disorders of visual perception in children born prematurely. Reason 2010 Meeting, July 2010, University of Warwick; The Edinburgh Perinatal Festival, The University of Edinburgh, May 2010; KT Poster Competition, Heriot Watt University, Edinburgh, April 2010.

Catriona Macintyre-Béon, Richard Bowman, Hussein Ibrahim, Julie Calvert, Gordon Dutton. Reliability of a question inventory for structured history taking in children with cerebral visual impairment. Royal College of Ophthalmologists Congress Meeting, Birmingham, May 2009; Yorkhill Hospital, Glasgow Audit Evening, Glasgow 2009; Reason 2009 Meeting, University of Warwick, June 2009; Child Vision Research Society Meeting, Cardiff, June 2009; BIPOSA Conference, Glasgow, September 2009.

Oral presentations

Catriona Macintyre-Béon, Richard Bowman, David Young, Gordon Dutton, Kate Mitchell, Judith Simpson, Ruth Hamilton. Perceptual Visual Dysfunction in Children Born Prematurely: Common But Easily Missed. Child Vision Research Society, Toronto, Canada, 15-17 June 2013.

Christine Gilbert, Catriona Macintyre- Béon, Richard Bowman, David Young, Gordon Dutton, Kate Mitchell, Judith Simpson, Ruth Hamilton. Perceptual Visual Dysfunction in Children Born Prematurely: Common But Easily Missed. 3rd World Congress on Retinopathy of Prematurity in cerebral visual impairment, Shanghai, October 14-16th 2012.

Kate Mitchell, Catriona Macintyre-Béon, Ruth Hamilton, Gordon Dutton. Prevalence and nature of perceptual visual dysfunction due to cerebral visual impairment in prematurely born children. Scottish Ophthalmic Club, Autumn Meeting, Stirling, September 2010.

Catriona Macintyre-Béon, Richard Bowman, Hussein Ibrahim, Julie Calvert, Gordon Dutton. Reliability of a question inventory for structured history taking in children with cerebral visual impairment. Scottish Ophthalmic Club. Spring Meeting, Stirling, February 2010.

Catriona Macintyre-Béon, Richard Bowman, Hussein Ibrahim, Julie Calvert, Gordon Dutton. Reliability of a question inventory for structured history taking in children with cerebral visual impairment, Neonatal Researchers Meeting (N3R), BLISS HQ, London, September 2009.

Catriona Macintyre-Béon, Richard Bowman, Hussein Ibrahim, Julie Calvert, Gordon Dutton. Reliability of a question inventory for structured history taking in children with cerebral visual impairment, Child Vision Research Society Meeting June 2009, Cardiff.

Richard Bowman, Catriona Macintyre-Béon, Hussein Ibrahim, Julie Calvert, Gordon Dutton. Reliability of a question inventory for structured history taking in children with cerebral visual impairment, Royal College of Ophthalmologists Congress, Birmingham, May 2009.

Abbreviations

ASQ – Ages and Stages Questionnaire

CVI - cerebral visual impairment

DSD - dorsal stream dysfunction

FFA – fusiform face area

fMRI - functional magnetic resonance imaging

HIE - hypoxic ischaemic encephalopathy

LGN - lateral geniculate nucleus

LBW - low birth weight

m - magnocellular

MRI - magnetic resonance imaging

MT – middle temporal lobe

p - parvocellular

PVL- periventricular leucomalacia

PVWMI - periventricular white matter injury

QMH – Queen Mother's Hospital

RHSC - Royal Hospital for Sick Children

ROP- retinopathy of prematurity

SC – superior colliculi

SCN – suprachiasmatic nucleus

SD – standard deviation

VA – visual acuity

VLBW - very low birth weight

VI - visual impairment

VSD - ventral stream dysfunction

WMDI- white matter damage of immaturity

Dedication

I would like to dedicate this thesis to my mum and dad, who sadly passed away and never got to see me complete the writing up of my research. To Graham and Fraser my two brothers who are no longer with us, I think of you all often and miss you terribly.

To Iona, Ross and Alice my children who are my constant inspiration.

17th February 2015

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Chapter 1 Introduction and overview of thesis

Cerebral visual impairment (CVI) and optic neuropathy are the commonest causes of visual impairment (VI) in children in developed countries (Hatton et al., 2007, Alagaratnam et al., 2002, Flanagan et al., 2003, Matsuba and Jan, 2006, Bunce and Wormald, 2008). Advances in obstetric and neonatal medical care have led to improved rates of survival in premature infants (Rudanko et al., 2003). In 1995 babies born at 25 weeks had a 55% chance of survival until discharge and in 2006 this had increased to 67% (EPICure, 2008). As prematurity is associated with CVI (Marret et al., 2007), it has in turn led to an increased prevalence of CVI (Reijneveld et al., 2006, McKillop et al., 2006, Williams et al., 2011).

Vision is of fundamental importance to child development. Vision more than any other sensory system provides detailed information about the surrounding world beyond the immediate body space (Milner and Goodale, 2006) allowing access to information, both in the immediate surroundings and in the distance. A large proportion of the brain is responsible for processing this visual information. Vision facilitates social communication and is responsible for visual guidance of movement, both of the upper limbs and of the body and lower limbs (Goodale and Milner, 2004). The development of these functions can be fundamentally impaired by damage to any part of the visual system which in turn can interfere with higher visual function development.

Babies who are born prematurely (<37 weeks) have not had time to fully develop *in-utero*. This has potential consequences for the visual system, for example developing retinopathy of prematurity (ROP) and/or periventricular leucomalacia (PVL) (Jacobson et al., 1998b). Babies born prematurely are at increased risk as blood and therefore oxygen has not reached all parts of the brain. PVL occurs when the white matter adjacent to the lateral ventricles is deprived of oxygen and the nerves in this area die, becoming soft, and scar tissue develops. Periventricular white-matter injury (PVWI) is the description of this feature when a premature baby's brain is scanned (Fazzi et al., 2004).

In addition, greater success in managing profoundly ill children has resulted in increased survival of children with meningitis (Ackroyd, 1984), encephalitis, and

hypoxic ischaemic encephalopathy (HIE), all of which can lead to CVI (Good et al., 1994). The event causing the CVI can also damage other areas of the brain, or the retina, optic nerves or optic chiasm resulting in the majority of children with CVI having additional impairments including ocular or neurological deficits.

The prognosis in CVI is uncertain and professionals working with families need to be realistic about a child's long-term visual potential.

Patterns of CVI have been identified resulting from malfunction of retrogeniculate brain structures serving vision (Good et al., 2001). CVI exists with various combinations of contributing deficits including: reduced visual acuities, restricted visual fields, visual disturbance from eye movement disorders, and cognitive and perceptual visual dysfunction (PVD) (Fazzi et al., 2004, Fazzi et al., 2005, Dutton and Jacobson, 2001). Affected children may have behavioural problems (Reijneveld et al., 2006), and educational support needs (Williams et al., 2011, Johnson et al., 2009). Often these children are labelled as clumsy, as they frequently bump into low objects such as coffee tables or trip over toys or obstacles which they do not appear to see. It can be difficult for affected children to find something on a patterned background or within a cluttered scene such as a toy box. They can have difficulty seeing things pointed out in the distance, possibly because the further away things are the more there is in the visual scene. They may not recognise friends and relatives and sometimes parents report that the children approach people that they do not know, mistakenly believing that they do know them. Problems splitting attention between two tasks is frequently reported by parents; for example, where affected children often trip and bump into obstacles when trying to walk and hold a conversation. Children with CVI may have difficulty attending to two tasks at the same time, so tend not to look at a speaker's face in order to concentrate on their verbal communication. This can be mistaken as rudeness as in Western society it is deemed discourteous not to look at the speaker's face. The observation of these patterns led to the development of a CVI questionnaire to aid in assessment of children (Dutton et al., 2010).

CVI is increasingly being recognised and acknowledged by the medical professions, and children with this diagnosis are able to be registered as visually impaired when historically they had gone undiagnosed (Bamashmus et al., 2004).

However, the frequency of CVI and its nature in high functioning prematurely born children are not known. Many of the children whose visual difficulties are described in this thesis manifest impaired cognitive and perceptual visual function ranging from subtle to profound difficulties.

Within this thesis, Chapter 2 provides a review of the literature identifying gaps in knowledge associated with CVI, and focussing on identification in children born prematurely. Chapter 3 discusses the study design and methodology. The fourth chapter presents the results of this study and Chapter 5 provides a discussion of the work, and a conclusion, suggesting future research in the classification of CVI and concluding with a description of the significance of the contribution this study has made on how children with CVI might be identified.

Chapter 2 Review of the Literature

Chapter 2 will give an overview of prematurity and its visual consequences including a description of normal visual development to aid understanding of CVI. Significant literature published relating to CVI and prematurity will be discussed. The study hypothesis and aim will conclude Chapter 2.

The literature review carried out for this study used OVID and included all years 1946 - 2014. The subject heading of "vision disorder" OR "cognitive disorder" gave 339 responses; limiting these to English, humans and children aged 2-12 years reduced this to 138. The article titles were read and if deemed relevant, abstracts were read. Further PubMed online search was carried out specifically reviewing CVI and questionnaires and questionnaire screening tools for identifying CVI in at risk populations.

2.1 Prematurity

Prematurely born neonates are at risk of cerebral palsy, hearing impairment, poor school performance, poor memory and autistic spectrum disorders (Ek et al., 1998, Aram et al., 1991, Teplin et al., 1991, The Scottish low birth weight group, 1992, Hack et al., 1995, Fily et al., 2006) as well as visual impairment.

The World Health Organisation (WHO) defines premature birth as occurring before 37 weeks' gestation. Table 2-1 defines the terminology used in relation to the gestation and weight at which a baby is born. Premature birth rates have been steadily rising since the early 1980s and 5-11% of infants are now born prematurely (Wen et al., 2004). The rate of premature birth in the UK has stayed around 7% since 1994, which equates to about 45,000 premature births each year or 125 each day (Norman et al., 2009).

Table 2-1 Definitions of frequently used terminology to describe infants who are born too early or too small (WHO, 2007).

Terminology	Definition
Premature baby	Born before 37 weeks
Moderately premature	Born between 35 and 37 weeks
Very premature	Born between 29 and 34 weeks
Extremely premature	Born before 29 weeks
Low birth weight baby	Weighs less than 2,500g (5.5lbs)
Very low birth weight baby	Weighs less than 1,500g (3.0lbs)

In Scotland preterm singleton births rose from 5.2% in 1975/76 to peak at 6.7% in 2003/04: more recent figures show that this has now fallen to 5.9% in 2011/12 (Scotland, 2013). In the United States, premature birth was described as a major US public health problem with a 30% increase from 1981 to 2004 from 9.4% to 12.5% (Allen, 2008, Behrman and Butler, 2006).

Improved neonatal care has resulted in the increased survival of premature infants (O'Connor et al., 2007, Jacobson et al., 2006, Cooke, 2006, Richardson et al., 1998); however, prematurity remains the principal cause of infant mortality and morbidity in industrialised countries (Wen et al., 2004), being responsible for 75% of such cases (Goldenberg et al., 2008, Ananth and Vintzileos, 2006). The high rate of infant mortality and low birth weight in the UK compares unfavourably with other major European nations: the UK had the highest infant mortality rate and only Greece had a higher percentage of low birth weight (UNICEF, 2007).

Obstetric intervention and the increase in artificially conceived pregnancies are two reasons for the steady rise in premature births (Ananth and Vintzileos, 2006, Joseph et al., 1998, Ananth et al., 2005, Goldenberg et al., 2008). The EPICure Study identified the following survival rates in 1995:

- babies born at 24 weeks: 30% chance of survival to discharge home.
- babies born at 25 weeks: 55% chance of survival to discharge home (Costeloe et al., 2000).

Since 1990, neonatal intensive care has improved (Hack et al., 1995) and in view of this the study was repeated. EPICure 2 identified significantly improved survival rates:

- babies born at 24 weeks: 47% chance of survival to discharge (17% increase)
- babies born at 25 weeks: 67% chance of survival (12% increase).

From 1995 to 2006, although survival of babies born between 22 and 25 weeks' gestation increased, the proportion of survivors with major neurodisability was similar (Moore et al., 2012, Costeloe et al., 2012).

Prematurity has been described as not a single disease but a complex condition resulting from multiple gene-environmental interactions that lead, through several pathophysiological pathways, to birth before 37 weeks gestation (Allen, 2008). Goldenberg et al. (2008) takes this idea a step further by describing premature birth as a syndrome initiated by multiple mechanisms including infection, inflammation and stress (Goldenberg et al., 2008).

Adverse medical and obstetric influences on premature labour include multifoetal pregnancies; 60% of twins are born prematurely (Goldenberg et al., 2008)), gestational/pre-existing diabetes (Sibai et al., 2000), intrauterine infection or urinary tract infection (Goldenberg et al., 2000).

Apgar scores have been used since 1952 to assess a newborn's condition at birth. Five easily identifiable characteristics, namely heart rate, respiratory effort, muscle tone, reflex irritability and colour are assessed and a value between 0-2 assigned at 1 minute and at 5 minutes and are a good indicator of the newborn's condition. Term-born and prematurely born infants have an increased survival rate as the Apgar score increases. Casey et al. (2001) reported in their study that although prematurely born infants had a low 5 minute Apgar score which reflected their gestational age, very low scores (0-3) were still associated with an increased risk of neonatal death.

Gender has an impact on risk of prematurity and male babies are at increased risk of being born prematurely, as well as having a higher incidence of fetal and neonatal mortality and being more vulnerable to long-term neurological and

motor impairments after preterm birth (McGregor et al., 1992, Harlow et al., 1996, Cooperstock and Campbell, 1996).

2.2 Visual consequences of prematurity

Prematurely born children have a higher incidence of disorders of the visual system than children born at term (O'Connor et al., 2007): incidence of visual abnormalities is 33-43% involving many areas of the visual system (Page et al., 1993, Gallo et al., 1991, Keith and Kitchen, 1983, van Hof-Van Duin et al., 1989, Tuppurainen et al., 1993).

2.2.1 Acuity

Acuity is about the same in healthier preterm infants as in their term born peers (Birch and Spencer, 1991, Norcia et al., 1987) but the presence of cortical insults in the sicker infants always results in poorer acuities than in term born or healthy preterm infants (Gibson et al., 1990, Norcia et al., 1987).

2.2.2 Retinopathy of prematurity (ROP)

ROP is a proliferative, inflammatory disease which attacks the developing retinal vessels during the perinatal period and which can cause blindness. The earlier that the preterm birth interrupts the vascularisation process, the greater the risk of acquiring the disease. Disease onset and progression relate to infant maturation with most cases of severe disease becoming evident between 34 and 41 weeks post-menstrual age (Fielder and Levene, 1992). Emerging data from BOOST II-UK, a world-wide randomised control trial, is showing that higher oxygen saturation ranges are associated with a higher risk of severe ROP; however the trials have also shown higher oxygen targets are associated with improved survival (Stenson, 2013, Fleck and Stenson, 2013, Group et al., 2013).

The preterm infant is also susceptible to neurological insults which can manifest as ophthalmic abnormalities such as nystagmus, optic atrophy and CVI resulting in poorer vision, binocular vision and poor visual acuity.

2.2.3 Ametropia

Discrepancy between the axial length of the eye and the optical power of its components leads to refractive error. Term-born infants typically have a slight hypermetropia (focussing beyond the retina) which diminishes through

emmetropisation (a visually guided growth process); by 12 months post-term, 95% of normal children are still hypermetropic.

The distribution of refractive errors in preterm infants is wide and shifted (relative to term born infants) towards myopia (focal length short of the retina) (Scharf et al., 1978, Dobson et al., 1981, Fledelius, 1981); at term age formerly preterm infants have mild hypermetropia compared to the moderate hypermetropia normally found in term infants (Snir et al., 2004). Hypermetropia is more prevalent overall than myopia (Ton et al., 2004). The incidence of myopia rises as gestational age falls; myopia is the norm in low-birth weight infants (<1000g) (Linfield, 1991).

Astigmatism is also more prevalent in former preterm infants, with 3-12% of ex-preterm infants (without ROP) having an astigmatism greater than two dioptres (>2D) at 30 months corrected age compared with 0.7% of a full term population (≥2.5D at 4 years) (Darlow et al., 1997, Holmstrom et al., 1999).

2.2.3 Strabismus (squint)

Around 5% of the general population is strabismic in early childhood, but this rises to 7-31% for ex-preterm infants during early childhood (Hungerford et al., 1986, Page et al., 1993, Pennefather et al., 1995, Fielder and Moseley, 2000).

2.2.4 Nystagmus

Nystagmus is a repetitive, involuntary, oscillation of the eyes. The condition might be caused by a developmental problem of the eye or brain, or the pathway between the two.

2.2.5 Optic neuropathy

Optic neuropathy refers to the death of the retinal ganglion cell axons that comprise the optic nerve resulting in pale optic discs on fundoscopy. Optic atrophy is an end stage that arises from myriad causes of optic nerve damage anywhere along the path from the retina to the lateral geniculate nuclei. Since the optic nerve transmits retinal information to the brain, optic atrophy is associated with vision loss.

2.2.6 Hypoxic ischaemic encephalopathy (HIE)

Perinatal hypoxic-ischaemia is a common cause of brain injury (Flodmark et al., 1990, Matsuba and Jan, 2006) and is caused by lack of oxygen. Neonatal HIE is caused by a blockage or rupture of a blood vessel in the brain that has many causes and risk factors including cardiac disorders, infection, maternal and placental disorders. In mild forms visual pathways may be spared, but more severe and extensive injury may affect regions such as the cranial nerve nuclei of the oculomotor nerves (affecting control of eye movement) and the lateral geniculate nuclei (affecting the visual input to the visual cortex) (Roland et al., 1986). Affected children might have problems with visual acuity, processing of visual information, nystagmus and strabismus (Flodmark et al., 1989, Lim, 1989). An estimated 60% of children with neonatal HIE have CVI (Good et al., 2001).

2.2.7 Periventricular white-matter injury (PWMI)

PWMI is the most common cause of brain injury in premature infants (Back, 2006, Volpe, 2000a, Ferriero, 2004). PWMI includes focal cystic necrotic lesions PVL and diffuse myelination disturbances. Neuroimaging studies indicate that the incidence of PVL is declining, whereas diffuse cerebral matter injury is the predominant lesion (Hamrick et al., 2004, Back and Rivkees, 2004, Miller et al., 2003, Inder et al., 2003, Counsell et al., 2003). PVL is the term used by neuropathologists on the post-mortem of brains, whereas PVWMI injury refers to the radiological findings (Flodmark and Jacobson, 2010). Lesions may not show on ultrasound scans in the neonatal period (Wheater and Rennie, 2000) but later MRI scans show PVWMI (Bracewell and Marlow, 2002). The periventricular areas carry information signals from the eyes to the vision areas of the brain. Scarring in these areas can slow or block passage of information which can in turn lead to CVI.

Many young children born prematurely show evidence of complex visual problems, which may manifest in any combination or degree, due to ROP (O'Connor et al., 2004, Fielder, 1998, Birch and Spencer, 1991), damage to the input pathways, pathology affecting the pathways responsible for interpreting what is seen, and abnormalities of eye movement (Fazzi et al., 2004, Jacobson and Dutton, 2000, Houliston et al., 1999, Dutton, 2003a).

Subtle disturbances in brain organisation of children born prematurely may be associated with poor school performance, demonstrated by several studies (Marlow et al., 2005, Hack et al., 1994, Powls et al., 1996).

2.3 Cerebral Visual Impairment

During the last 20 years studies have focussed increasingly on CVI and its implications for affected children. In order to set the scene for the complexity of CVI the following section describes the normal developing visual brain.

2.3.1 Normal brain development

The nervous system develops through a series of synchronised processes. Some of these are completed before birth while others continue into adulthood (Waugh and Grant, 2006). The outermost layer of the embryo (ectoderm) gives rise to the central and peripheral nervous systems as well as the epidermis (Waugh and Grant, 2006). The major events in human brain development include primary neurulation (at 3-4 weeks gestation), i.e. development of the neural tube, and prosencephalic development (at 12-16 weeks) which differentiates the forebrain and facial structures at one end from the spinal cord at the other.

In the developing brain the neurons proliferate near the ventricles then migrate to the areas where they will settle into their final neural circuits. Normal brain development is dependent on the signals transmitting to the correct location thereby ensuring the cerebral hemispheres, cerebellum and brainstem develop in the correct anatomical region of the brain (Volpe, 2000b, Walsh, 2000, Suzuki, 2007). Migration is largely complete by 22-24 weeks gestation (Nadarajah et al., 2003).

The organisational events which occur during gestation, and in some cases continue until adulthood, are:

- establishment and differentiation of the sub-plate neurons
- alignment, orientation and layering of cortical neurons
- elaboration of dendritic and axonal ramifications
- establishment of synaptic contacts
- cell death, selective elimination of neuronal processes, synapses and proliferation and differentiation of glia (Volpe, 2000a, Pomeroy and Kim, 2000).

Beginning during the second trimester (13-27 weeks) of pregnancy and continuing into adulthood is the formation of the myelin sheath around axons (Volpe, 2000a). Myelination starts at the spinal cord and brainstem proceeding to the cerebrum and cerebellum; the most rapid changes occur during the first eight months postnatally (Suzuki, 2007).

From 24 weeks of gestation until term (40-42 weeks), each cortical neuron will establish approximately 1000 synaptic connections, creating the great bulk of cortico-cortical connections within the cerebral hemispheres. Wyatt describes this as the flowering of the dendritic tree (Wyatt, 2007). Within the human central nervous system it is estimated that there are approximately 10^{11} neurons and 10^{10} synapses (Wyatt, 2007) (Table 2-2).

Table 2-2 Major events in human brain development and peak times of occurrence (Volpe, 2000a).

Major developmental event	Peak time of occurrence
Primary neurulation	3–4 weeks of gestation
Prosencephalic development	12–16 weeks of gestation
Neuronal proliferation & organisation	22-24 weeks of gestation
Myelination	12–27 weeks continuing into adulthood

Insults occurring at varying stages of brain development may cause brain damage. Three important factors are involved: the stage of brain development at insult; the severity of the insult; and the duration of the insult. The timing of the insult in relation to the developmental stage of the brain is the principal element in the resulting damage leading to long-term developmental problems (Jacobson and Flodmark, 2010).

The timing of insult in relation to the stage of pregnancy and the processes of development of the visual system occurring at this time may result in the infant having a wide range of visual problems from total blindness to limited visual

perception of light (Krageloh-Mann et al., 1999). Visual outcomes following insult at differing stages of pregnancy are summarised in Table 2-3.

Table 2-3 Visual outcomes following insult at different gestational ages (Jacobson and Flodmark, 2010).

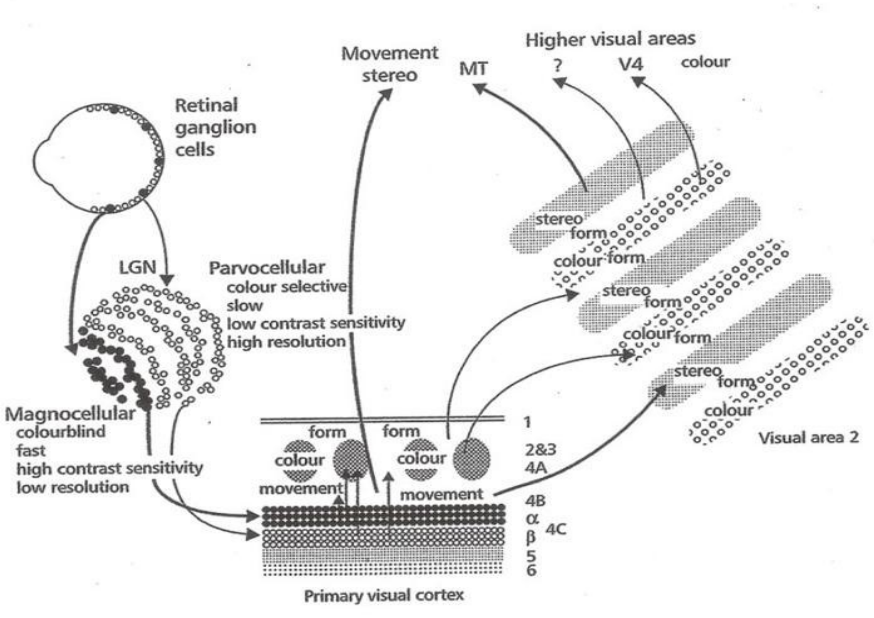
Timing	Stage of development	Visual outcomes
First trimester (weeks 1-12)	Cell proliferation	Optic nerve hypoplasia and septo-optic dysplasia (which may also be due to excessive apoptosis) (Barkovich et al., 2001).
	Abnormal neuronal migration	Varies from total blindness to delayed and limited visual maturation, often with strabismus and nystagmus (Barkovich et al., 2001)
Second trimester (weeks 13-27)	Impaired cortical organisation	Can result in homonymous hemianopia (Tychsen and Hoyt, 1985)
Third trimester (weeks 28–42) Early third trimester (≤ 34^{+6} weeks)	Damage <34 weeks gestation results in white matter damage of immaturity (WMDI) including periventricular leucomalacia (PVL) and secondary to intraventricular haemorrhage.	Severe VI with low acuity, ocular motility dysfunction, altitudinal inferior visual field defects and severe cognitive visual problems through to early onset esotropia or slightly subnormal visual acuity (Volpe, 2000 (b), Olsen et al., 1997)
Late third trimester (>35 weeks)	Profound asphyxia may lead to severe cranial nerve dysfunction and athetoid or dyskinetic cerebral palsy (Krageloh-Mann et al., 1999)	The extent of damage determines the severity and localisation dictates whether and how vision is affected. Middle cerebral artery infarction often results in homonymous visual field defects (Krageloh-Mann et al., 1999).

2.3.2 Normal visual anatomy

The process leading to the perception of an image by the brain, sight, is extremely complex. Light enters the eye and is refracted by the cornea. It passes through the pupil (controlled by the iris) and is further refracted by the lens. An image of the external scene is projected on the retina by the cornea and lens which accommodates to focus the inverted image.

The retina transduces the light striking the photoreceptors into physiological signals which combine information from myriad rod and cone photoreceptors onto the receptive fields of the parvocellular (p) and magnocellular (m) ganglion cells (Livingstone and Hubel, 1988). Thus, some image processing takes place prior to the signals leaving the eye en route to the brain (Figure 2-1).

Figure 2-1 Schematic diagram showing the anatomical and functional distinctions between the magnocellular (m) and parvocellular (p) pathways. MT, middle temporal area; V4, visual area 4; LGN, lateral geniculate nucleus (dorsal part). The differential projections to the lower layers and the subdivisions (stripes) in visual area V2 are shown (Livingstone and Hubel, 1988) (Reproduced with permission from Science).



The image data from the retina passes to the primary visual cortex via the ganglion cells of the retina which leave the eye as the optic nerve. The primary

visual cortex (also known as the striate cortex or area V1) is located in the occipital lobe (the rearmost portion of the brain). There is a visual cortex in each hemisphere of the brain. Nasal retinae nerve fibres cross over at the optic chiasm while the temporal retinal fibres remain on the same side (Livingstone and Hubel, 1988). At the optic chiasm, outputs from the two eyes combine and image data from the right side of both eyes are passed to the left side of the brain for processing and vice versa (Holmes, 1918b).

The afferent pathways (the retina, optic nerve, optic tract, optic chiasm and retrochiasmal pathways, including optic radiations and the cortical/higher cognitive areas of visual representation) synapse in the six layered lateral geniculate nucleus (LGN), which selectively transfer the magnocellular and parvocellular data to the retrogeniculate pathways of the primary visual cortex (V1) (Goodale and Milner, 1992).

The visual information is carried via the optic radiations which separate into three portions: the upper, lower and central bundles (Meyer, 1907). Fibres receiving data from the superior retina (upper bundle) travel straight back superior and adjacent to the lateral ventricles to the superior visual cortex, while the central bundle contains only macular fibres and leaves the lateral geniculate body in a lateral direction and follows posteriorly along the lateral ventricular wall to the visual cortex. Fibres from the inferior retina pass through the temporal lobes by looping around the inferior horn of the lateral ventricle (Meyer's loop) carrying information from the superior part of the visual field (Barton et al., 2005) to the inferior visual cortex.

2.3.3 The higher visual system

The brain is responsible for analysing and understanding what we see (Goodale and Milner, 2004, Dutton, 2003a, Trobe and Bauer, 1986). Primary visual processing takes place in the occipital lobes. Neuroimaging studies have confirmed that visual projections from primary visual processing areas involve a separation into ventral and dorsal streams (Grill-Spector et al., 2004, 2008). Ventral and dorsal streams are associated with perception and action, respectively. Many studies involving monkeys support the distinction between perception and action (Glickstein et al., 1998). A series of retinotopic areas have

been mapped out beyond the primary visual cortex (V1) including V2, V3, V4, and V5 (MT) and an area specialised for colour processing (V8) in the human extrastriate cortex using fMRI (Table 2-4) (Tootell et al., 1996, Hadjikhani et al., 1998). Higher visual processing involves recognition and orientation which take place in the temporal lobes. Visual guidance of movement and parallel processing of the visual scene for visual search takes place in the posterior parietal territory. Recognition is a conscious process while visual guidance of movement is subconscious (Goodale and Milner, 2004, Milner and Goodale, 2006, McKillop et al., 2006, Grüsser and Landis, 1991, Dutton and Jacobson, 2001).

Early studies on understanding the organisation of the higher visual system arose from behavioural and neuropsychological studies of brain-damaged humans and monkeys (Glickstein et al., 1998, Lund et al., 1975, Goodale et al., 2004). Studies using fMRI have strengthened the evidence of a two–stream model of visual processing as well as giving insight into the functional complexities of the dorsal and ventral streams (Culham and Valyear, 2006). A summary of the main functions, structures and locations of primary visual processing are described in Table 2-4.

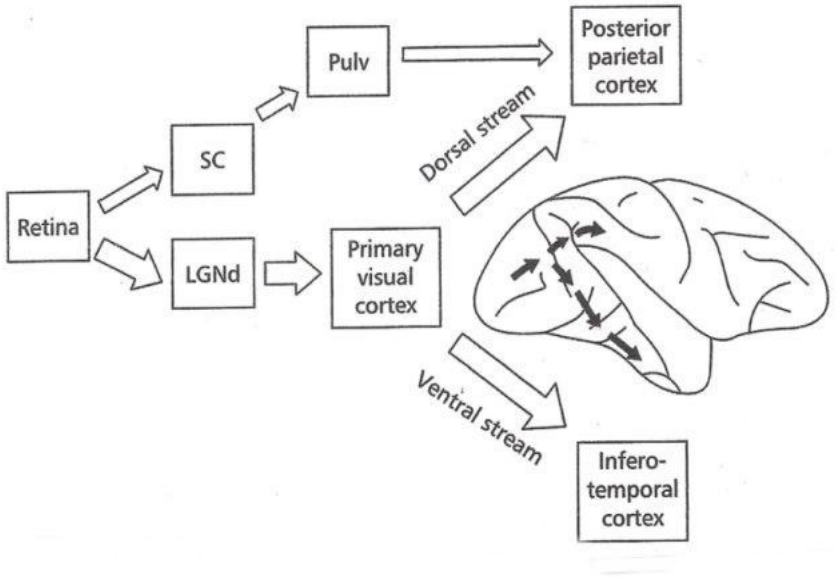
Table 2-4 Summary of the main functions of the primary visual processing areas in the brain.

Area	Function	References
LGN	a sensory relay nucleus in the thalamus consisting of six layers known as the primary processing centre	(Dreher et al., 1976)
SC	processes subconscious peripheral visual function	(Sparks, 2002)
SCN	responsible for controlling circadian rhythms	(Frisch, 1911)
Pulvinar	deals with higher order visual and visuomotor transduction	(Grieve et al., 2000)
Pretectum	receives inputs from the retina as well as being involved in the control of the pupil	(Simpson, 1984)
V1	through the cortical hierarchy of V2, V3, V4, and V5, area V1 is responsible for transmitting information to the dorsal and ventral stream pathways	(Livingstone and Hubel, 1988)
V2	four quadrants with dorsal and ventral stream representation sub serving object recognition and attentional modulation	(Gazzaniga et al., 2002)
V3	Area V3 located immediately in front of V2 has a role in processing global motion	(Braddick et al., 2001)
V4	selective attention firing rates in V4 could be as much as 20%; also responsible for colour information and is directly involved in form recognition	(Tootell and Hadjikhani, 2001), (Zeki and Marini, 1998), (Moran and Desimone, 1985)
V5	responsible for processing visual motion	(Born and Bradley, 2005)
V8	specialises in colour processing (extrastriate cortex)	(Simpson, 1984)

In 1982 Ungerleider and Mishkin proposed the concept of two broad streams of projections from the primary visual cortex in which there is a splitting of visual information into two anatomically-related streams. They examined the selective effects of lesions in the brain of the macaque monkey. The dorsal stream (which they called the "object-channel") passes from the primary visual cortex (V1) in the occipital lobe forward into the parietal lobe and became known as the "where" pathway, responsible for processing information regarding where an object is in visual space. The ventral stream (which they called the "spatial

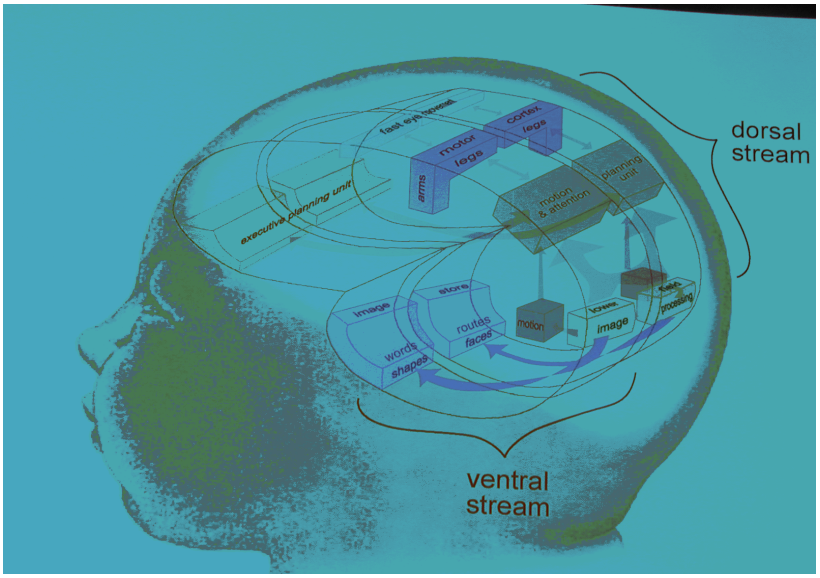
channel") runs from the primary visual cortex to the inferotemporal lobes and became known as the "what" pathway, specialising in perceiving different aspects of the visual world (Ungerleider and Mishkin, 1982) (Figure 2-2).

Figure 2-2 Major routes whereby retinal input reaches the dorsal and ventral streams ; SC: superior collicus (SC), pulvinar (pulv), lateral geniculate nucleus dorsal (LGNd), (Goodale and Milner, 2006) (Reproduced with permission from the Oxford University Press).



In 1992, Goodale and Milner agreed with the concept of the anatomical differences between the dorsal and ventral streams and confirmed that the ventral stream processed information for perception (Figure 2-3), while the dorsal stream processed information for action (Goodale and Milner, 1992). This was supported by later work with a patient in which the authors concluded that the requirements of perception and action required different transformations of the visual signals (Goodale and Westwood, 2004).

Figure 2-3 Stylised diagram showing the location and functions of the dorsal and ventral streams (Dutton, 2003a). (Reproduced with permission from Eye).



Rizzolatti and Matelli (2003) proposed a dorsal stream organisation, with the superior regions of the posterior parietal cortex responsible for the on-line control of action and the inferior regions of the posterior parietal cortex being responsible for multiple object awareness (Rizzolatti and Matelli, 2003). Jeannerod and Jacob (2005) developed the above definition by proposing that the parietal lobe had three distinct areas with different functions: the superior parietal lobe responsible for carrying out visuomotor processing (the on-line control proposed by Rizzolatti and Matelli (2003)); the right inferior parietal lobe contributing to the perception of spatial relationships and the left inferior parietal lobe related to visually goal-directed action (Jeannerod and Jacob, 2005).

2.3.3.1 The dorsal stream

The dorsal stream connects the occipital lobes to three brain areas: the posterior parietal lobes (which process the visual picture and attention to specific aspects of the picture), the motor cortex (which allows movement through visual space) and indirectly to the frontal cortex including the frontal eye fields (which allows attention to be paid to specific aspects of the scene, by

generating rapid head and eye movements to specific aspects of the scene) (Dutton, 2003a, Goodale and Milner, 1992).

Dorsal stream dysfunction (DSD) has been increasingly recognised as a disorder in children with damage to the brain (Hansen et al., 2001, Atkinson et al., 1997, Spencer et al., 2000, Dutton and Jacobson, 2001, Fazzi et al., 2004) associated with a range of pathologies affecting the posterior parietal area, ranging in character and severity. It may be associated with slightly or significantly impaired visual acuities and visual fields. It is common in children with periventicular white matter injury, those born very preterm, and in those with Williams syndrome (Atkinson et al., 1997, Fazzi et al., 2004).

Visual processing of motion takes place in the middle temporal area, also called MT or area V5 (Maunsell and van Essen, 1983) and is responsible for perception of fast movement. This motion perception is linked to the dorsal stream (Figure 2.3) and area V5 receives input from the eyes via the magnocellular pathways through the LGN (Lund et al., 1975, Maunsell and van Essen, 1983). Although area V5 has traditionally been associated with the dorsal stream, this motion-sensitive area has been shown in both monkeys and humans to have a strong functional relationship with both visual streams (Felleman and Van Essen, 1991). This led Milner and Goodale to believe that area V5 plays a role not just in visually mediated guidance of movements but also in the recognition both of moving objects and the characterisation of actions such as that of a galloping horse (Milner and Goodale, 2006, Pavlova et al., 2003).

Perception of movement is a subconscious, constant, fluid process linking to the dorsal stream, guides movement through three dimensional space, with the internal map constantly being matched to the external reality (Dutton and Bax, 2010). The dorsal stream also interacts with the subcortical movement perception system, comprising the SC, pulvinar of the thalamus and the balance system, served by the inner ear structures and labyrinthine nuclei (Atkinson, 2000).

A frontal-parietal circuit relating to hand object manipulation was initially identified in the anterior intraparietal sulcus (Binkofski et al., 1998), demonstrating that in order to grasp an object, the anterior bank of the

intraparietal sulcus is required for visual control of object-directed grasping movements (Culham et al., 2003). The manipulation required to pick up an object is brought about by the interconnecting pathways of the dorsal stream in which the picture is formed in the occipital lobes and mapped by the parietal lobes. The choice of what to pick up is a frontal function. The action is then executed through the motor cortex. The parietal reach region (PRR) is situated along the medial bank of the intraparietal sulcus (area MIP) and the parieto-occipital sulcus (area V6A). This region mediates the visual control of reaching movements (Connolly et al., 2003).

Apart from clinical observation of the behavioural outcomes of posterior parietal damage (Holmes, 1918, Dutton et al., 2004), there is little or no identifiable literature concerning the brain sub-systems which bring about visual guidance of movement of the lower limbs and body.

The posterior parietal lobe has been implicated in attention and is responsible for integrating information from more than one sense, selectively ignoring relevant information and focusing on the target of interest. Attention is a broad term, but is thought to comprise several sub-systems (Posner and Petersen, 1990). Impaired visual attention is a common manifestation of cerebral dysfunction. In adults, closed head trauma, cerebral microvascular ischaemia and dementia are common causes (Das et al., 2007). In children, aetiologies include periventricular white matter pathology, hydrocephalus, hypoxic ischaemic encephalopathy, and brain damage caused by hypoglycaemia. Visual search and visual attention are commonly impaired in children with DSD (Posner and Petersen, 1990, Manly et al., 2001). Visual search and visual attention entail subconscious analysis of the visual scene while at the same time processing incoming data from other sensory inputs (Corbetta et al., 1998, Das et al., 2007). Subsequent conscious choice is served by the frontal territory (Corbetta, 1998).

An area deep in the lateral bank of the intraparietal sulcus comprises three networks: the posterior superior parietal area, the middle inferior parietal area and the anterior inferior parietal area, identified using fMRI, and have been acknowledged as having the primary role of visual control of saccadic eye movements (Connolly et al., 2003). This area links to the saccadic eye

movement generator in the frontal eye field. It has been suggested that that humans have a similar organisation scheme as that of monkeys in areas involved in hand eye processes; these are situated lateral to those selectively involved in hand-eye movement (Connolly et al., 2000).

The posterior parietal cortex also integrates information input from senses other than vision. For example, watching a football match is a complex task; while watching the player who has the ball, it is possible to select another player and immediately change gaze and attention to this second player. Added to this complex scene is the background noise of the crowd cheering. The posterior parietal lobes are responsible for controlling this complex integration, which also facilitates participation in the live scenario. A person is not aware of the total visual scene at any one time, but selects, attends to and samples parts of it (Atkinson, 2000). Although the experience of the external world appears to be smooth and complete, this is an illusion, because it is the integration of multiple, selective sampling which leads to a sense that the elements sampled are holistic in nature.

2.3.3.2 The ventral stream

The ventral pathway runs from the occipital lobe to the occipitotemporal and temporal lobes on each side of the brain (Goodale and Milner, 1992). The temporal lobes subserve colour, object recognition and visual memory as well as being responsible for providing a rich and detailed representation of the world. They facilitate recognition of objects and faces, accurate orientation and navigation by means of recognition, and a sense of direction (Goodale and Westwood, 2004).

Work on understanding the functional organisation of the ventral stream has been ongoing since the 1960s. Goodale and Milner made significant progress in understanding the nature of ventral stream processing and they demonstrated on monkeys that the visual neurons in the ventral stream areas were not modulated by the motor activity of the monkey.

Malach et al. (1995) identified an area in the occipital lobe specialising in the processing of objects, which is known as the lateral occipital area. Other studies

have since confirmed this and clarified the lateral occipital area's role in object perception (Grill-Spector et al., 1998).

The fusiform face area (FFA) can be found in the right fusiform gyrus confirmed by fMRI. It was demonstrated that activation occurred more by pictures of faces than by any other picture types. The FFA has been shown to be quite separate from other areas in the parahippocampal gyrus which are activated by pictures of buildings and scenery (Kanwisher et al., 1997).

Children who have damage to the ventral pathways may experience problems with route finding, both when outside and in familiar buildings such as school (Stasheff and Barton, 2001, Greene, 2005, Grüsser and Landis, 1991, Dutton, 2003a).

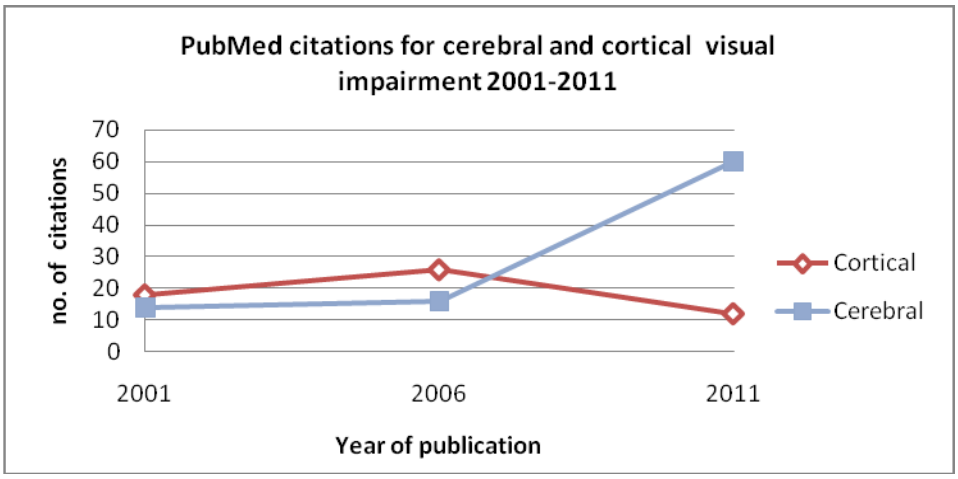
Simian experiments have shown that within the inferotemporal cortex and neighbouring superior temporal sulcus there are cells that are tuned to specific objects and object features maintaining their selectivity irrespective of view point, retinal image size and even colour (Logothetis and Sheinberg, 1996). The idea that cells in this region might play a role in comparing current visual inputs with internal representations of recalled images was put forward in 1992 (Eskandar et al., 1992). Images may be stored in other regions such as the neighbouring medial temporal lobe (Squire et al., 2007).

2.3.4 Diagnosis of CVI

CVI is the commonest form of VI in children in the developed world (Flanagan et al., 2003, Hatton et al., 2007). In North America, the C of CVI is often interpreted as cortical rather than cerebral. Both interpretations (cortical and cerebral) use the anatomical location as a classifier of the condition. Cerebral VI is differentiated from ocular VI which may be caused by other conditions such as congenital cataracts or retinal disorders. Brain white matter, such as the optic radiations, is not part of the cortex, and PVL (injury to white matter of the brain) is a frequent finding in children with cerebral VI. The term cerebral is therefore a more inclusive term than cortical (Colenbrander, 2005, Colenbrander, 2010, Good et al., 2001, Good, 2009), and has been used throughout this study as the working interpretation.

A PubMed search for “cerebral visual impairment” and “cortical visual impairment” between the years 2001 and 2011 showed a semantic shift in the use of terminology describing CVI with the term cerebral VI growing and the phasing out of the use of the term cortical VI (Figure 2-4).

Figure 2-4 PubMed citations for cerebral and cortical visual impairment 2001-2011.



Failure to diagnose CVI can result in educational delays or emotional problems; for example, being unable to find a friend in the playground can lead to social isolation (Sonksen, 1993). Developmental milestones that require vision (reaching and walking) are often delayed in children with CVI in the absence of other disabilities (Moller, 1993).

The EPICure study 2009 reported that prematurely-born children are at higher risk than their term-born peers in requiring special educational support. Furthermore this requirement is likely to increase as children born prematurely reach secondary level education (Johnson et al., 2009). These findings have recently been corroborated by the Avon longitudinal study, which reported that children with visual perceptual difficulties were more likely to under-achieve in reading and mathematics. However, with simple interventions, some children were able to reach their full potential (Williams et al., 2011). Strategies and interventions will be discussed in more depth in section 2.3.8. Children with CVI

may also have behavioural and educational support needs (Reijneveld et al., 2006, Johnson et al., 2009, Williams et al., 2011).

White matter damage of immaturity (WMDI) was shown to affect the visual fields of all six subjects tested by Jacobson et al., (2006), aged between 13-25 years, and who had been born at a gestational age of 28-34 weeks. WMDI was confirmed by MRI scan. Subjects were examined with manual and computerised quantitative perimetry which confirmed that all subjects had subnormal visual field function. The lower visual field was more commonly affected than the upper visual fields. In particular, the image resolution in the lower visual field was poor, prompting the authors to surmise that fewer incoming fibres serve a wider area.

Prevalence studies of CVI to date may not have included mild forms of the disorder, and may even underestimate the disorder. A Northern Irish study identified 76 visually impaired children from a total population of 47,110. Forty-three percent of those identified with VI had additional global developmental delay and severe learning difficulties, 33% had cerebral palsy and 45% (34 children) were diagnosed with cortical VI (Colenbrander, 2010). Only 22% of those identified with VI were registered blind or partially sighted with the Department of Health, indicating that prevalence data based on statutory records under-represent CVI caused by damage to the brain (Flanagan et al., 2003).

During the four-year period January 2000 to December 2004, data captured on the USA 'Babies Count' register of VI children aged 0-3 years found cortical VI to be the commonest form of the VI. Of the sample 2,155 children had a VI and approximately 40% were registered legally blind, and 68% had difficulties in addition to VI. Cortical VI, ROP and optic nerve hypoplasia were the three most prevalent visual conditions (Hatton et al., 2007).

This increased identification of CVI (whether cortical or cerebral) is likely to be due to both increased recognition and diagnosis of the problem as well as a possible true increased incidence due to greater survival rates of at-risk premature infants and those sustaining damage to the brain. Sub-classification of CVI, for example into disorders of primary image processing, of visual acuity or visual field, as well as those affecting higher visual functions served by the

dorsal and ventral streams might aid diagnosis through clearer recognition of how this disease is manifest and aiding in the development of habilitation strategies for children (or re-habilitation if the child previously had vision but lost it through infection such as meningitis).

Perinatal hypoxic-ischaemic brain injury is the commonest cause of CVI in term and prematurely born children (Flodmark et al., 1990, Eken et al., 1995, Matsuba and Jan, 2006). The terminology over the past decade with respect to CVI has changed. CVI is becoming a more frequently used term as it is more specific to the anatomical areas of damage and outcome for those affected.

2.3.5 Dorsal stream dysfunction (DSD)

Malfunctioning of the dorsal stream pathway results in DSD. Visual acuity is commonly reduced but can be normal (Saidkasimova et al., 2007, Good et al., 1994, Gillen and Dutton, 2003). Colour vision and contrast sensitivity are usually normal, and if there has been superior posterior periventricular damage, children with CVI commonly have bilateral lower visual field impairment (Dutton and Jacobson, 2001). Rarely, impaired or absent perception of movement can result from damage to the middle temporal lobes on both sides which lie anterior to the visual cortex (Milner and Goodale, 2006). The following features have been noted in DSD:

Visual field impairment or impaired visual attention to one side

Visual field loss may present if damage occurs to any part of the visual pathway. If the damage is before the optic chiasm the field loss is ipsilateral; if after the optic chiasm, the field loss is contralateral to the lesion because the optic nerves partly cross over at the optic chiasm (Pipe and Rapley, 1997).

Impaired perception of movement

Features include the inability to see details of moving objects, and dislike of cartoons and other fast moving imagery. Children with CVI often describe moving objects such as dogs or footballs suddenly appearing or disappearing. They may also struggle to count fingers on a moving hand unless it is moved very slowly (Saidkasimova et al., 2007,Houliston et al., 1999, Pavlova et al., 2006).

Difficulty with handling a complex visual scene

A common characteristic of DSD is the inability to see an obvious feature pointed out in the distance. This may not be simply due to reduced visual acuity but also due to the greater complexity of a scene viewed at a distance (Milner and Goodale, 2006). Young children may be unable to select a chosen toy from a toy-box or a crowded cupboard or may have difficulty in finding and picking items up from a patterned carpet (Dutton and Jacobson, 2001).

Impairment of visually guided movement of the body

Impaired visual guidance of movements is particularly evident for the lower limbs; a typical feature is not knowing whether a floor boundary is a step. Specific problems include the inability to switch between floor coverings e.g. carpet onto tiles in an adjoining room without prior tactile exploration; lifting the feet too early or too late, for example when anticipating kerb heights; walking off the edge of kerbs without seeing them; difficulty negotiating stairs, especially descending, without the aid of a banister to provide tactile and proprioceptive clues to the gradient (Saidkasimova et al., 2007). Lower limb guidance problems may be seen in children with lower visual field defects even when looking directly down and are thus probably not entirely attributable to the visual field defect (Saidkasimova et al., 2007, Dutton et al., 2004, Houliston et al., 1999, Dutton, 2003a). Inaccuracy in visually guided movement of the arms may lead to a tendency to knock things over (Good et al., 2001).

Impaired visual attention

Impaired visual attention is a common manifestation of DSD. Recent reviews have highlighted attention problems as a focus of particular concern related to premature birth (Mulder et al., 2009, van de Weijer-Bergsma et al., 2008). Particular difficulty arises with splitting attention between two tasks; for example walking while talking can lead to bumping into obstacles or needing to hold a hand (Mulder et al., 2010, Dutton et al., 2004, Saidkasimova et al., 2007).

Pagliano et al (2007) found evidence of specific DSD in prematurely-born children. In a series of children with spastic diplegia they found greater visuo-perceptual impairment and specifically visuo-motor impairment in premature subjects, when compared with age-matched children born at term, although

general cognitive performances were equal. In contrast to Jacobson's and Fazzi's work, the term and pre-term children had similar MRI findings, leading the authors to conclude that the prematurity may have adversely influenced the reorganisation of visual centres and pathways following the initial developmental insult, but without manifest pathology on imaging (Jacobson et al., 2003).

2.3.6 Ventral stream dysfunction (VSD)

Malfunctioning of the ventral stream pathway in the temporal lobe territories results in VSD (Goodale and Milner, 2004). In 2001 it was reported that many patients had bilateral lesions involving the occipito-temporal areas, while in some it was only the right side that was damaged which led the author to believe that the right side of the brain may be dominant for facial recognition (Goldsmith, 2001). Recognising faces is a complex task; first we must perceive the face, and then image data must pass via the ventral stream to the fusiform gyrus where comparison with stored data takes place to seek a match. If a match is found, the face is recognised (Carey, 1992, Sergent et al., 1992). The following features have been noted in VSD:

Impaired ability to recognise faces (prosopagnosia)

Difficulties with face recognition usually become obvious around school age (Goldsmith, 2001). Prior to this, children can recognise family and friends by their voices. A child with CVI and good visual acuity may mistake a stranger for a parent (Dutton et al., 2006).

Problems with route finding (topographic agnosias)

A person cannot rely on visual cues to guide them directionally due to the inability to recognise objects. Nevertheless, they may still have an excellent capacity to describe the visual layout of the same place. Patients with topographical agnosia have the ability to read maps, but become lost in familiar environments (Grüsser and Landis, 1991).

Problems with object and shape recognition (visual form agnosia)

Goodale and Milner described visual form agnosia following carbon monoxide poisoning in a patient who suffered severe bilateral damage to her ventral stream in the lateral occipital areas while retaining the use of her dorsal stream.

The patient had the ability to accurately guide hand movements to pick up objects but was unable to identify the objects (Goodale and Milner, 2004). Work by James et al (2003), using fMRI examining dorsal and ventral stream activation during object recognition and object directed tasks, confirmed that visual form agnosia was associated with extensive damage to the ventral stream (James et al., 2003).

2.3.7 Definition of CVI for this study

The working definition of CVI in this study is a disorder of the process required to decode incoming information, recognising that visual perception, cognition and attention constitute an integrated system. This definition is very inclusive and acknowledges that previous studies (Fazzi et al., 2007, Olsen et al., 1997, Dutton et al., 2004) have described this symptom complex, now termed CVI. A greater understanding of the issues that reduce affected children's ability to cope with day-to-day activities is desirable. Early detection is on the increase which in turn will lead to strategies being developed and worked on both pre-school and in the early years of primary and secondary education (Dutton, 2013, Williams et al., 2011).

2.3.8 Suggested management of children affected by CVI

Strategies have been developed which help children make day-to-day activities less daunting (Tables 2-5 and 2-6) (McKillop et al., 2006).

Many children described a fear of, or lack of inhibition in, crowded environments such as supermarkets. Parents revealed that behaviour and attention may improve in less crowded and undecorated environments (McKillop et al., 2006). Older children have described that reading can be enhanced by enlargement and optimal spacing of text, while masking adjacent text or presenting text one word at a time on a computer screen can prove an effective strategy for those with more severe problems (Dutton et al., 2004, Houliston et al., 1999, Dutton, 2003a, Saidkasimova et al., 2007, Dutton, 2013).

Table 2-5 Dorsal stream strategies (McKillop et al., 2006).

Clinical manifestation	Recommendations
Inability to handle complex visual scenes	
Difficulty finding a toy in a toy box.	Store toys separately.
Finding an item on a patterned background.	Use plain carpets, bedspreads and decoration.
Finding an item of clothing in a pile of clothes.	Store clothes separately in clear compartments.
Seeing a distant object (despite adequate acuity).	Get close. Share a zoom video/digital camera view
Impaired perception of movement	
Upper limbs: Inaccurate visually guided reach.	Occupational therapy training
Lower limbs: Feeling with the foot for the height of the ground ahead at floor boundaries. Difficulty walking over uneven surfaces (despite full visual field, and looking down).	Provision of tactile guides to the heights of the ground ahead. For example pushing a toy pram or holding on to the belt pocket or elbow of an accompanying adult.
Impaired visual attention	
Difficulty 'seeing' when talking at the same time, which may cause a child to trip or bump in to obstacles.	Limit conversation when walking.
Behavioural difficulties	
Marked frustration at being distracted.	Limit distraction by reducing background clutter.

Table 2-6 Ventral stream strategies (McKillop et al., 2006)

Clinical manifestation	Recommendations
Impaired recognition	
Difficulty recognising faces. Incorrectly recognising people who are unknown.	Family and friends introduce themselves and wear consistent identifiers. Training to identify and recognise identifiers.
Impaired orientation	
Problems with route finding outside.	Training in orientation.
Difficulty with route finding within buildings, for example, school.	Training in orientation.
Problems with orientation within a room and not knowing which cupboard or drawer to open.	Training in orientation.
Difficulty recognising objects and shapes.	Training in tactile recognition as well as visual.

2.3.9 Structured clinical history-taking questionnaires

Structured history-taking is a foundation of medical practice. While the questioning strategies for many medical diagnoses are internationally recognised and applied there are no standardised question sets for CVI.

The characteristics of an established developmental assessment questionnaire (Ages and Stages Questionnaire [ASQ]) were assessed by Skellern et al. in 2001. The research team were looking for an effective screening tool to be used on a population of prematurely born infants at high-risk of visual problems. Underpinning their study was the desire to ensure all children were being identified for developmental testing at the earliest possible age to maximise the child's potential and ensure limited resources were being used in the best possible way. The authors analysed the data collected from the ASQ from the Development Clinic at the Mater Children's Hospital in Brisbane, Queensland, Australia; 136 questionnaires were returned completed (81%) and were

compared to formal psychometric assessment (Griffith Mental Development Scales for 12-24 months, Bayley Mental Development Intelligence Scale for 18-months, McCarthy General Cognitive Intelligence Scale for 48-months). Developmental delay was considered to be present if any of the above psychometric assessments fell below 1.0 standard deviation (SD). The ASQ cut-off used was 2.0 SD. Their results for all age groups demonstrated the ASQ had 90% sensitivity, 77% specificity and a negative predictive value of 98%; which they concluded supported the use of the ASQ as an effective screening tool for cognitive and motor delays in their follow-up of prematurely born infants. A similarity between their study and the present study was the desire to involve parents in the assessment process. The ASQ questionnaire had 5 sub-sections assessing communication, gross motor, fine motor, problem solving and personal social development. The CVI questionnaire used in the current study is similar in design as it has 7 sub-sections assessing visual behaviours. Although different statistical analysis was performed in each study, the measuring of the sensitivity, specificity and reliability were similar and the process of engaging parents would encourage their on-going involvement and participation in their child's care by them having a greater understanding of appropriate strategies which would enhance day to day living for the children and their families (Skellern et al., 2001). The work by Skellern et al. (2001) supports the aim in the present study to identify prematurely born children at risk of CVI.

Dutton and colleagues developed a 58-item questionnaire which was sub-divided into 7 sub-sections. Each sub-section of the questionnaire contained several questions designed to probe the same aspect of vision (Dutton and Bax, 2010, Macintyre-Beon et al., 2012). This history-taking questionnaire was used to explore visual dysfunction in children and to contribute to clinical refining of CVI. The questions/sections are derived from clinical experience, but independent verification by standard procedures used to validate subjective rating scales has not yet been undertaken. Further work is needed to validate this questionnaire and perhaps one of the best models to do this is the Rash analysis (Rasch, 1960) as it evaluates and reframes subjective rating scales, can estimate interval scale from ranking responses, eliminating redundant items and provide for useful combinations, eventually leading to a refined measure of behaviour.

A tool to test the screening utility of another questionnaire for CVI has been developed and tested by Orbitus. They correlated the questionnaire results with diagnostic tools (L94, the Test of Visual Perceptual Skills – Revised (TVPS-R) and the Visual Perception (VP) subtask of the Beery test of VisuoMotor integration) (Beery, 1997). Subjects were recruited following referral to the CVI clinic, a tertiary referral centre for children with visual perceptual problems. Parents of the 91 children recruited to the study completed the 46 closed items which were presented in a binary scale of 'yes' or 'no' responses exploring different characteristics of CVI (Ortibus et al., 2011a,b).

This questionnaire by Ortibus' group was developed using work from Dutton and colleagues (Dutton, 2003b) which formed the basis of their 46-item questionnaire. Many of the questions were adapted from the CVI questionnaire used in the present study; three further areas were developed with respect to complex problems, other senses and associated characteristics. The strength of the work carried out by Orbitus is that it investigates psychometric properties and validity (although not using Rasch model) and analyses sensitivity/specificity with respect to standard visual perceptual tests. Parents completed the questionnaire prior to evaluation and its score was correlated with examination and testing results. Statistical analysis showed the tool to have good predictive value for identifying children at risk of CVI. This is the most appropriate published work to date to aid identifying children with CVI.

Genderen et al. (2012) retrospectively investigated the clinical characteristics of 30 children with good visual acuity and CVI and compared them with 23 children who had been referred with a suspicion of CVI but proved to have a different diagnosis. They concluded that CVI in children remains primarily a clinical diagnosis that should be based on the presence of known causes of CVI in the medical history, as this proved to be the most important factor. Genderen et al., (2012) like Dutton et al., (2010 supported the use of questionnaires if identifying the various features of CVI in children with a suspect medical history; however, they concluded that they should not be used for screening purposes as they yield too many false-negatives (Genderen, 2012, Dutton and Bax, 2010). The finding of Genderen et al. (2012) supports the hypothesis of the current study as prematurity increases the risk of children developing CVI.

A recent review by Lehman was carried out as a result of recent developments in questionnaires being developed and tested for reliability in an attempt to identify those children at risk for CVI (Lehman, 2012). It is stated in the review that the definition of CVI is constantly evolving and being modified and accepts that CVI now includes vision-guided motor planning and higher level executive functions. However, the review defines CVI as cortical visual impairment, which could limit the general ability of the review.

Summary

Visual impairment is detrimental to child development. CVI is the commonest cause of VI in the developed world but it continues to be undetected in many children. Terminology used to describe CVI is moving towards more precise descriptive terms which might aid in the identification and classification of affected children.

Increasing awareness of CVI and improving recognition of the signs and symptoms will enable children to be identified earlier and allowing appropriate strategies to be put in place to improve quality of life at home and at school. Prematurely born children are at higher risk than their term-born peers of developing CVI. CVI appears to be often characterised by DSD comprising some or all of the following: impaired perception of movement; difficulty handling the complexity of a visual scene; impairment of visually guided movement of the body; impaired visual attention. VSD features may also be present, comprising some or all of the following: impaired ability to recognise faces (prosopagnosia); problems with navigation or route finding (topographic agnosias); problems with object and shape recognition (visual form agnosia). As discussed above CVI is constantly evolving with respect to definition and means of identifying children at risk.

Prematurity can also cause significant visual problems for children. Although premature birth is recognised as a cause of CVI, a review of the literature highlights that prematurity and the incidence and nature of CVI has not been studied in detail on a prematurely born cohort of children. This present study wishes to address this gap in our knowledge.

2.3.10 Aim of Study

Study hypothesis: Children born prematurely are at increased risk of CVI.

Aim of study: To identify whether children born prematurely are at increased risk of CVI.

Chapter 3 Study design and methodology

Overview

This controlled study was designed to assess whether 46 children who were born prematurely and attending mainstream education were at increased risk of CVI as identified by a CVI questionnaire (Appendix 1) developed by Dutton and

colleagues at the Royal Hospital for Sick Children, (RHSC), Glasgow. Extensive optometric, ophthalmic, IQ and visual function testing was also undertaken.

3.1 Approvals and data protection

Ethical approval for the prematurely born children for this study was granted by West of Scotland Ethics Committee 1, REC reference number: 08/S0703/105. The 130 control children were a sub-set of children recruited to a separate but related study (Dorsal stream dysfunction in children: characterisation, identification, and management, Dr J Calvert et al., Medical Research Scotland, Ref: 106FRG). Ethical approval for investigation of the control children was granted by the School of Health and Social Care Ethics Committee, Glasgow Caledonian University and external ethical approval (R&D) was granted through the NHS Director of Research, RHSC, Glasgow Research Ethical Committee ref: 06/50708/15 for the control participants and the children.

All subjects were assigned a code to maintain confidentiality and anonymity. All personal details relating to the participants were securely stored in a locked filing cabinet, the researchers involved in the study being the only people with access to these details, thus adhering to the Data Protection Act 1999.

3.2 Recruitment

Prematurely born children

The prematurely born children in this study were born at the Queen Mother's Hospital (QMH) in Glasgow between 1996 to 2000, at less than 37 weeks gestation and were attending mainstream education. Eligible participants were identified by Dr. B Holland, Consultant Neonatologist at the Queen Mother's

Hospital, Glasgow. Those identified were or had been attending a developmental clinic[1] with no neurodisability at any stage. The invitation to consider participating in the study was extended by a member of the clinical team either directly at the developmental clinic or by letter. Every potential participant received an information sheet and consent form outlining the study. An information sheet was designed for parents of children aged under 8 years (Appendix 2) and another for children aged 8-12 years (Appendix 3). In all cases the parents were given the information sheet; children aged >8 years were also offered one and one was filed in the child's casenotes. For children who had not had hospital contact for some time, their General Practitioner or Health Visitor was contacted initially to ensure that it was appropriate to contact the family and then letters of invitation were sent (Appendix 4). Those wishing to participate were contacted by the researcher and a mutually convenient time was agreed for assessment. GPs of all children who participated in the study were informed (Appendix 5).

Inclusion criteria: Born at less than or equal to 37 weeks gestation; attending mainstream education.

Exclusion criteria: VA worse than 0.775 logMAR; congenital/ophthalmological defects, co-morbidity, neurodisability identified at the neonatal developmental follow-up clinics (Figure 3-1); additional learning support at school.

Parents were given the opportunity to ask questions after receiving the information sheet. Once children/parents were happy to proceed, consent/assent was taken with a copy being given to the family and a further copy filed in the child's case notes.

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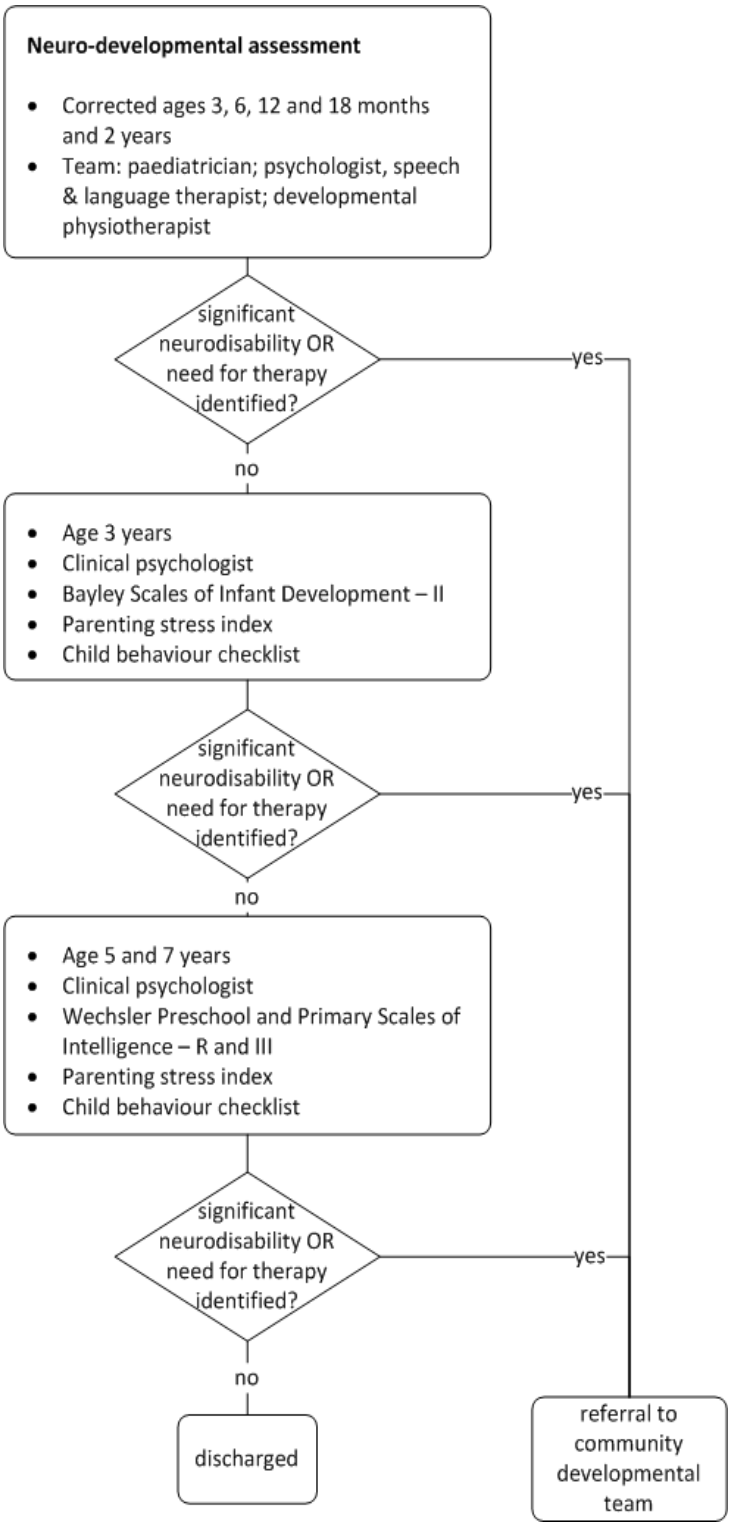
[1] A neurodevelopmental clinic at the Queen Mother's Hospital (QMH), Glasgow at which prematurely born children are seen at corrected ages of 3, 6, 12 and 18 months, and at 2 years by a neonatologist, a psychologist, a speech and language therapist and a developmental physiotherapist. Children who have no identifiable neurodisability at 2 years are subsequently seen again at 3 years when a clinical psychologist performs the Bayley Scales of Infant Development BSID-II, limited to the mental scale (BAYLEY, N. 1969. *Bayley Scales of Infant Development,* New York, Psychological Corporation. Parenting Stress Index, and the Child Behaviour Checklist) and then at 5 and 7 years (Wechsler Preschool and Primary Scales of Intelligence WPPSI-R and WPPSI-III, Parenting Stress Index, and the Child Behaviour Checklist) (Figure 3-1). If significant neurodisability is identified at any stage, referral to a community-based developmental clinic is offered. Neuro-ophthalmic referral is offered if any parent has concerns about their child's vision.

Figure 3-1 Flowchart illustrating routine clinical process for identifying neurodisability.



Controls

The 130 control children were identified from children receiving mainstream education from seven primary schools in East Dunbartonshire in the age-appropriate school years for comparison with the study group. The Head of Education for East Dunbartonshire Council gave permission to contact head teachers of local schools (Appendix 6, Appendix 7). A meeting was held with each head teacher who agreed to participate, at which the study was explained in more detail and logistics were discussed e.g. working around the school day and liaising with class teachers to minimise disruption. Inclusion and exclusion criteria were also discussed.

The head teacher identified eligible participants at each school using the agreed inclusion and exclusion criteria. Every potential participant's parents received a letter and information sheet outlining the study which they were asked to sign and return if they agreed their child could participate (Appendix 8); a letter (Appendix 9) was sent to GPs of all subjects who participated.

Inclusion criteria: no known ophthalmological history or developmental disorders; not receiving additional educational support; born at term (>37 weeks gestation).

Exclusion criteria: poor reading skills, dyspraxia, autism, any other developmental or behavioural disorder medically diagnosed as reported by parents or teachers.

3.3 General methods

All children (46 prematurely-born study children and 130 control children) had the CVI questionnaire (Appendix 1) completed by their parents, seeking behavioural features of seven aspects of CVI. All underwent visual perceptual testing, comprising visual closure, global form assessment, global motion assessment and the Stirling face recognition test. All underwent visual attention assessment comprising the four subtests of the Test of Everyday Attention for Children (TEA-Ch): i) selective attention ("Sky Search") with a motor control task; ii) attentional control/switching ("Opposite Worlds"); iii) sustained attention ("Score!") and iv) sustained-divided attention ("Sky Search DT").

Visual acuity (section 3.6.3) and stereoacuity (section 3.6.4) were measured in control children at the start of the session to screen for children with subnormal acuity (>0.1 logMAR) or stereoacuity (<120'). This also gave an opportunity to ensure the child was able to read and understand the tests they were to undertake.

The prematurely-born subjects were tested in a quiet room at the RHSC. The control children were tested in a quiet room at school (medical room or classroom), and playtime and lunchtime breaks were incorporated into the testing schedule as agreed with teachers and parents. A assessment lasted from 25 to 45 minutes depending on their age; older children were able to complete the tasks in a shorter time.

3.3.1 Additional tests for the prematurely born children only

3.3.1.1 Ophthalmic assessment

To account for confounding ophthalmic problems on any CVI, the study group also underwent: visual acuity testing (Keeler crowded and uncrowded logMAR 3 metre test and bar reading test at 30 cm); colour vision using Ishihara plates, the City University Colour Vision Test, and the Modified Panel D15 test; contrast sensitivity (Peli-Robson test at 1 m); stereoacuity (Frisby Stereotest); Goldmann perimetry (14e target) where possible; eye movement assessment and cover tests for manifest or latent strabismus. Case records provided obstetric, neonatal and paediatric histories. Ophthalmic testing and case review were undertaken by Dr. K Mitchell, paediatrician, RHSC. Details of the test methods used are given in section 3.6.

3.3.1.2 IQ assessment

As low non-verbal IQ is a common characteristic of children with early brain damage, it was important to assess whether IQ confounded results of the visual tasks (Stiers et al., 1999) and the prematurely born group therefore underwent IQ testing, (section 3.7).

3.4 CVI questionnaire

The seven areas probed by the CVI questionnaire were:

a) visual field impairment or impaired visual attention to one side

b) impaired perception of movement

c) difficulty with handling complexity of a visual scene

d) impairment of visually guided movement of the body

e) impaired visual attention

f) difficulties associated with crowded environments

g) difficulties with recognition and navigation

A full list of questions in each section is given in Appendix 1.

Prematurely born children

The parents of the prematurely born children were asked to complete the CVI questionnaire whilst the researcher (CMB) carried out the visual perceptual, attention and IQ tests. After these tests were completed and results documented, the responses given on the CVI questionnaire were discussed with the parents, with particular emphasis on probing positive responses. This was done in a quiet room at RHSC. The researcher was therefore masked to the questionnaire responses during the visual perceptual, attention and IQ testing. The ophthalmic testing and case note review was similarly masked to the questionnaire responses.

Controls

Parents of control children completed the CVI questionnaire at home.

3.5 Visual perceptual and attention tests

Tests were selected to assess presumed dorsal (attention, simultaneous perception, and global motion) and ventral stream functions (face recognition and global form). A broad attempt was made to correlate the asserted tested sub-system with those functions explored in each of the seven sub-sections of the CVI questionnaire. This was partly as an exploratory design in case any one test had results which correlated strongly with the CVI questionnaire findings and therefore could be further explored as a tool for identifying CVI. The descriptions of individual tests are presented in the order of the subsections of the CVI questionnaire A-G.

An overview of the CVI question numbers by subsection, the probed underlying visual function and the possibly correlated selected test is shown in Table 3-1. The tests are then described in detail, by section. Test scores were recorded on a Test score sheet (Appendix 10).

Table 3-1 Summary of questions and subsections of the CVI questionnaire mapped to the visual function and assessment tests used.

Subsection	Questions seeking evidence of:	Assessment battery test used
A Q's 1-13	Visual field impairment of impaired attention on one or other side	Attentional tests
B Q's 14-18	Impaired perception of movement	Global motion
C Q's 19-27	Difficulty handling the complexity of a visual scene	DTVP subset closure
D Q's 28-36	Impairment of visually guided movement of the body and further evidence of visual field impairment	Global motion
E Q's 37-40	Impaired visual attention	Attentional tests
F Q's 41-44	Behavioural difficulties associated with crowded environments	Attentional tests
G Q's 45-51	The ability to recognise what is being looked at and to navigate	Face recognition and global form

3.5.1 Subsections A, E and F: questions assessing attention

Subsection A had 13 questions seeking evidence of visual field impairment or impaired attention on one or other side; subsection E had four questions seeking evidence of impaired visual attention, and subsection F had four questions seeking evidence of behavioural difficulties associated with crowded environments (split attention). These aspects were assessed using four subtests of the Test of Everyday Attention for Children (TEA-Ch).

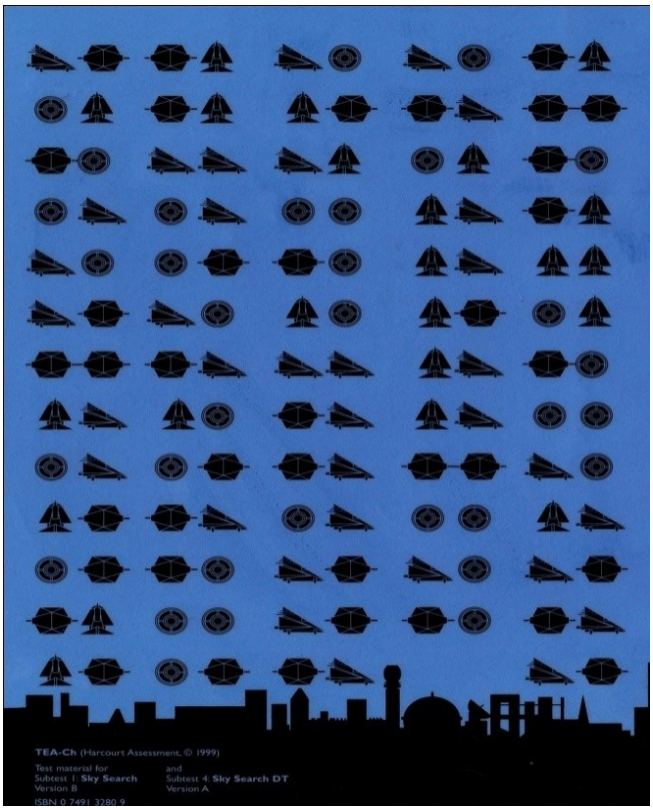
Attention is defined by Atkinson as the ability to deploy the resources of the brain so as to optimize performance towards behavioural goals (Atkinson, 2000). Deficits in prematurely-born children's ability to direct and maintain attention have been reported (Du Plessis and Volpe, 2002, Mulder et al., 2009, Mulder et al., 2010). Visual attention assessment for this study comprised four subtests of the Test of Everyday Attention for Children (TEA-Ch) (Manly et al., 2001), which consist of nine subtests adapted from the adult literature covering the attentional subsystems (Posner and Petersen, 1990). It was designed specifically for children from six to 16 years, and demands on memory, reasoning, task comprehension, motor speed, verbal ability and perceptual acuity are kept to a minimum. In addition, performance on the TEA-Ch is independent of IQ. The following four subtests were used in the present study:

1) selective attention ("Sky Search") with a motor control task;
2) attentional control/switching ("Opposite Worlds");
3) sustained attention ("Score!");
4) sustained-divided attention ("Sky Search DT").

3.5.1.1 TEA-Ch: Selective attention measures ("Sky Search")

Children are given a laminated A3 sheet depicting rows of four distinctive types of paired spacecraft with 108 mixed type pairs (distractors): they are asked to find the 20 identical pairs (targets) as quickly as possible (Figure 3-2). The child marks a box in the corner when finished and both speed and accuracy are scored. A practice A4 sheet is done first to ensure comprehension of the task.

Figure 3-2 Stimuli for the Sky Search and Sky Search DT subtests of the TEA-Ch. Children are asked to search for identical pairs of spacecraft. (Reproduced with permission from Pearsons).

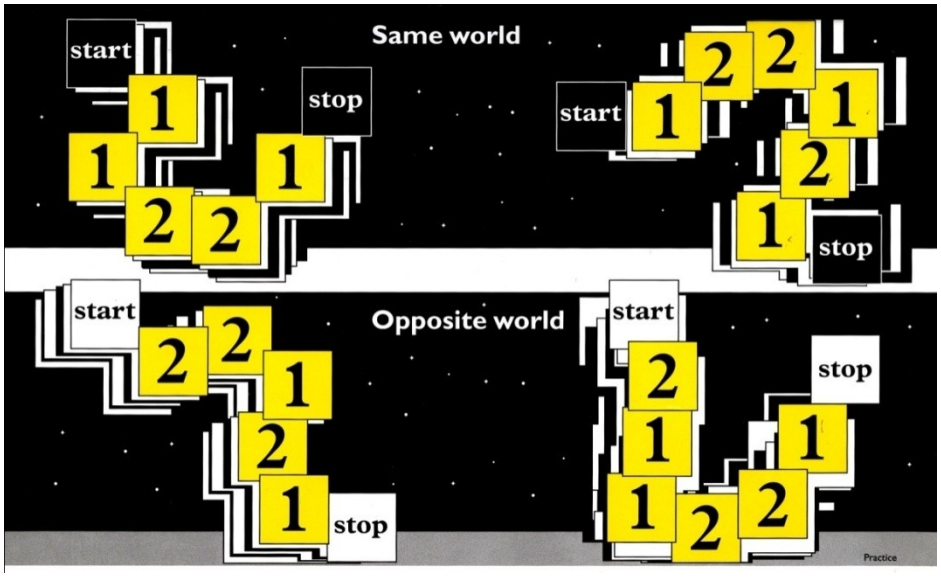


In order to control for differences that are attributable to motor speed rather than visual selection, the children then completed a motor control version of the task. The same A3 stimulus sheet is shown but with all distracter items removed. The child is asked to circle the 20 target items as quickly as possible and then indicate completion. Time taken to completion and accuracy recorded for both parts of the test. A time-per-target score (time/targets found) is calculated for the first task, and the time-per-target score from the motor control task is subtracted to produce an attention score that is relatively free from the influence of motor slowness or clumsiness.

3.5.1.2 TEA-Ch: Attentional control/switching ("Opposite Worlds")

The aim is to make the association between the numbers and the words as explicit as possible by using the digits 1 and 2 as the stimuli and the words 'one' and 'two' as the response options. In the first task ("Same World" condition), children are shown a stimulus sheet with a mixed, quasi-random array of the digits 1 and 2 (Figure 3-3). They are asked to read the digits aloud as quickly as possible in the conventional (matching) manner, to reinforce the prepotent set of naming the numbers in the conventional manner in the context of the test materials, and also to identify any unexpected difficulties a child may experience with the task. In the second task ("Opposite world" condition), they are asked to say the opposite for each digit ('one' for 2 and 'two' for 1) as quickly as possible, inhibiting the prepotent verbal response. During the task, the examiner points to each digit in turn, only moving onto the next when a correct response is given, thus turning errors into a time penalty. Following practice in each condition, four test pages are run in this order: "Same world"; "Opposite World"; "Opposite World"; "Same World". Total time for the Opposite World condition was taken as the dependent variable.

Figure 3-3 "Opposite world" Subtest of THE-Ch showing the practice examples given to the children to confirm their understanding of the test instructions. Reproduced with permission from TEA-Ch.



3.5.1.3 Sustained attention measures ("Score!")

Sustained attention requires the active maintenance of a particular response set under conditions of low environmental support (e.g. when there are few triggers to the relevant behaviour or when the task lacks interest or reward). The Score! subtest is a 10-item tone-counting measure (Wilkins et al., 1987). In each item, between 9 and 15 identical tones of 345 ms duration are presented, separated by silent inter-stimulus intervals of variable duration (between 500 and 5000 ms). Children are asked to count silently the tones (without assistance from fingers) and to give the total at the end, as if they were "keeping the score by counting the scoring sounds in a computer game". If a child was unable to count to 15 or was unable to pass two practice trials (with relatively few tones) the test was not given, and recorded accordingly as too difficult. The requirement to pass practice items provided the means of ensuring task comprehension, checking on possible sensory problems and improving the reliability of the measures, and was a feature of each of the tasks (Manly et al., 2001). The 10-item tone counting is recorded following each game (Figure 3-4) and total number correct out of ten is the recorded score.

3.5.1.4 TEA-Ch sustained/divided (dual task) measure ("Sky Search DT")

Performance decrements under dual task conditions tend to form sensitive measures of neurological impairment (Baddeley et al., 1991, Stuss et al., 1989). The TEA combines two of its subtests to form a dual task measure which was used in this study. In the Sky Search DT test, children were asked to complete a parallel version of the Sky Search task (Figure 3-2), differing only in the locations of the targets. As they performed the visual search they were asked simultaneously and silently to count the number of tones presented within each item of an auditory counting task, giving the total at the conclusion of each item. The counting task used the same stimuli as the Score! Subtest but with a regular pacing of one tone per second. Following practice, the task and timing were initiated by an auditory countdown. The test ended and timing stopped when the child indicated completion of the visual search component. Scores from both measures were incorporated into a total score in case a child neglected one of the tasks and the time taken to find each visual target (total time/correctly identified targets) and the proportion of correctly counted tones (total items correct/total items attempted) were both calculated. Counting

performance was then used to inflate the time-per-target score. Finally, the original Sky Search time-per-target score was subtracted from this value.

[Example: a child took 89 seconds to complete the Sky Search DT task during which he found 19 targets. His time-per-target score was therefore 89/19=4.68. He gave correct totals to three of the six tones; his proportion of correct scores was therefore 3/6 = 0.5. Dividing his Sky Search DT time-per-target score by this proportion inflates his time-per-target score to 4.68/0.5 = 9.36. In his original Sky Search test, his time-per-target score was 3.2 seconds. Subtracting this from his Sky Search DT, the dual weighted time-per-target score gives the decrement value 9.36-3.2 = 6.16.]

3.5.2 Subsections B and D: questions assessing perception of movement and visually guided movement of the body

3.5.2.1 Global motion

Subsection B had 5 questions seeking evidence of impaired perception of movement and subsection D had 9 questions seeking evidence of impairment of visually guided movement of the body. These aspects were assessed using a global motion assessment, which measures integrated motion signals across space. A screen-based system was used, and children were asked to identify or guess the predominant direction of motion of moving dots, either up, down, right or left. There was no time limit. Each coherence level was repeated eight times. Stimuli were black dots on a grey background (density = 1.1dots/deg^2; contrast =98%; dot profile=circular symmetric D4; peak spatial frequency =3.6cpd). Dots translated at a speed of 3.1°/ were redrawn on each frame (frame refresh rate of 60Hz) and had a lifetime of 3 frames, after which they were replaced by a dot at a random position. Dots translated within a circular window of 17.4° diameter (Braddick et al., 2000, Atkinson et al., 2003).

The test finished when an observer's response did not exceed chance (25%) on two successive coherence levels. The resulting data were fitted with a Quick function (Quick, 1974) using a maximum likelihood procedure and thresholds were defined as the point on the psychometric curve equivalent to 62% correct responses. Stimuli were displayed on a laptop computer and viewed from

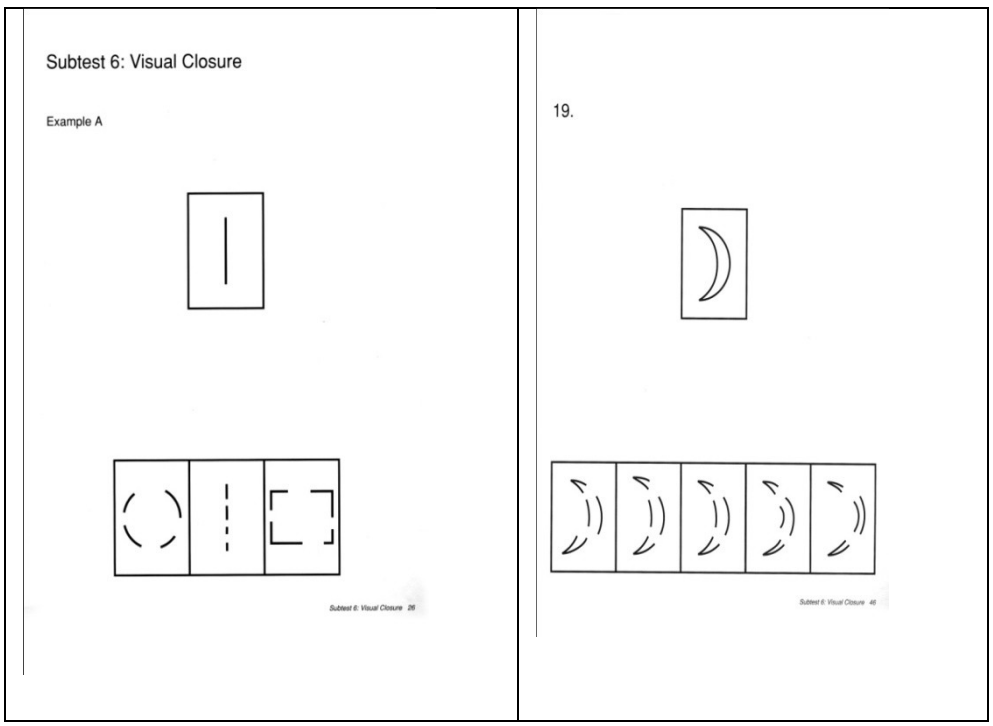
approximately 40cm (visual angle = 43.6°x 29.1°; pixel size of 2.04 arcmin). Percentage thresholds were displayed and recorded.

3.5.3 Subsection C: questions assessing difficulty with handling visual complexity

3.5.3.1 Developmental Test of Visual Perception-Children (DTPV): subtest "closure"

Subsection C had 9 questions seeking evidence of difficulty handling the complexity of a visual scene. This aspect was assessed using the Developmental Test of Visual Perception-Children (DTPV), 2nd edition, subtest of closure (Manly et al., 2001). This test is designed for children from 4 to 12 years, and required the children to match a figure to an array of similar figures with components omitted (Figure 3-4, Example A). Raw scores (out of 20) were converted to age-independent standard scores (Hammill et al., 1993) removing age effect. Question 19 of the closure test (Figure 3-4) shows the increasing complexity of the figures presented to the children.

Figure 3-4 The Developmental Test of Visual Perception-Children (DTPV), subtest closure. Example A: practice sheet to ensure understanding of instructions; question 19 shows the increasing complexity of the figures. (Reproduced with permission from DTVP).



3.5.4 Subsection G: assessing difficulties with recognition and navigation

Subsection G comprised 7 questions seeking evidence of difficulties recognising what is being looked at or difficulties with navigation (ventral stream). These aspects were assessed using a face recognition test and a global form test.

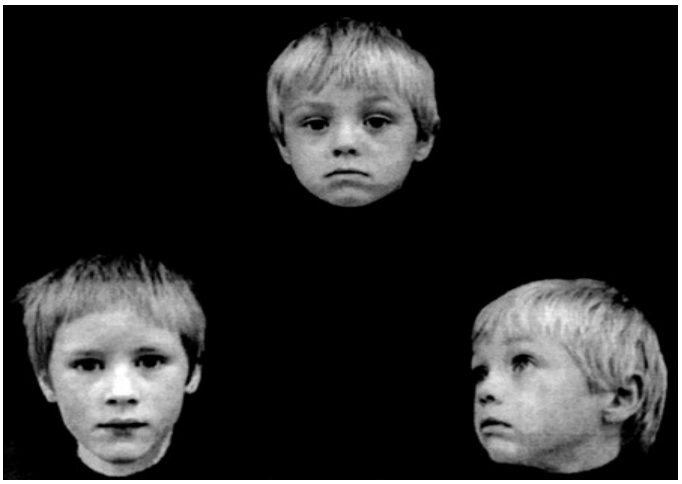
3.5.4.1 Facial recognition

The Stirling Face Recognition (SFR) is a card-based, face recognition test for children aged 4-10 years. The identity matching tests were used in this study. The children were shown black and white photographs of a target face and two test faces, and asked to decide which of the two faces matched the target face (Figures 3-5 i-iii) (Bruce et al., 2000, Bruce and Young, 1986).

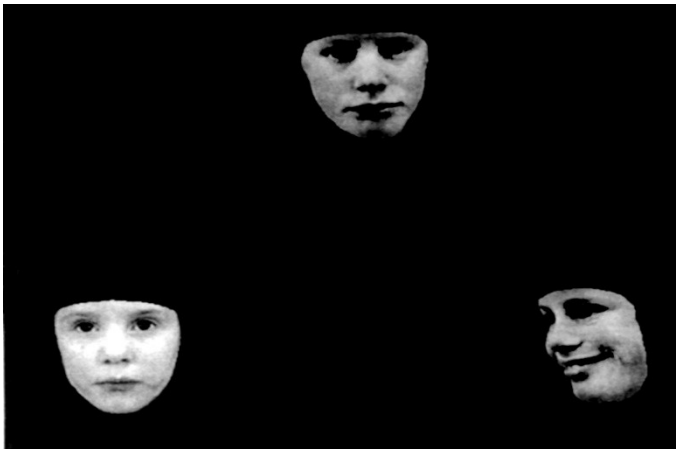
Three different tests are available with increasing difficulty, each having 16 trials. If the children identify three consecutive faces incorrectly the test was stopped. The first test (ID-Sim) showed similar faces (e.g. the distracter face was the same sex, and of similar age and overall appearance). The second test (Dis-masked) was the same as the first (ID-Sim) but with hair and ears concealed, and the third test (Sim-masked) was the same as the first (ID-Sim) but with hair, ears and eyes concealed.

Figure 3-5 Stirling face recognition test (Reproduced with permission from Stirling University).

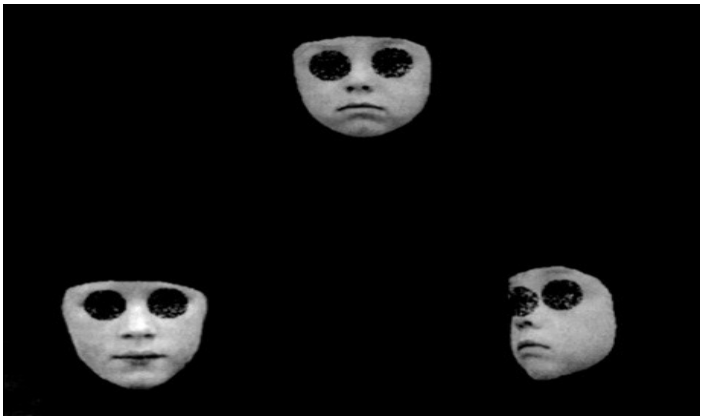
(i) ID-Sim: shows similar faces



(ii) Dis-masked: eyes and ears concealed



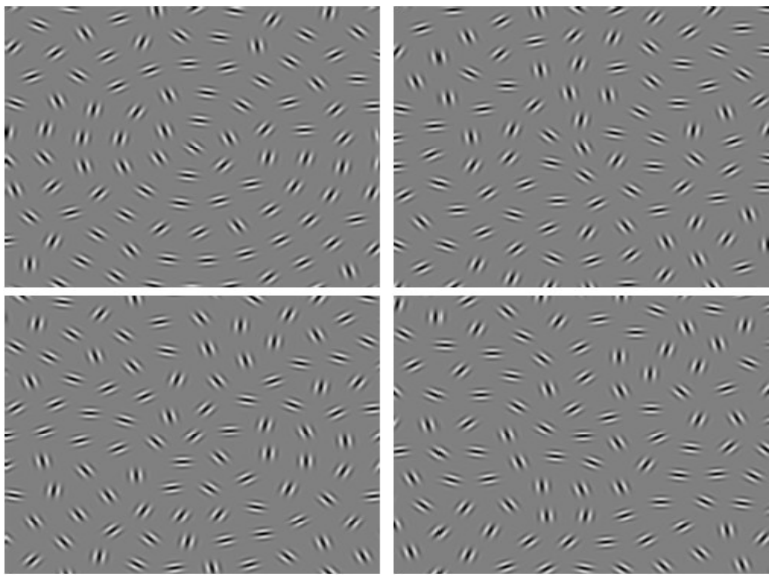
(iii) Sim-masked: hair, ears and eyes concealed



3.5.4.2 Global form

The global form assessment determines the ability to integrate position and orientation information from elements (oriented Gabors) distributed within a stimulus array. Children were asked to identify (or guess if unsure) which of four squares presented contained the concentric circles (form) (Figure 3-6). Stimuli were displayed on an LCD screen viewed from 40cm (visual angle = 43.6°x 29.1°; pixel size of 2.04 arcmin). No time limit was set. The task determined the minimum threshold coherence (percent of signal element relative to noise) required to detect the target (form) (Achtman et al., 2003, Loffler et al., 2007). The four choice paradigm presented had a descending method of limits testing at coherence levels from 100% to 0.4%. Each coherence level was repeated four times. The test ended when the lowest coherence was reached or if the observer's response did not exceed chance (25%) on two successive coherence levels. A psychometric function was fitted to the data and thresholds defined as the point at which observers were correct in 62% of the trials.

Figure 3-6 Global form stimuli: The form stimulus consists of four square arrays (14.3° x 14.3°) each containing oriented Gabors (N=150 on average, contrast=98%; peak spatial frequency=3.6 cycles per minute; envelope size=0.167°; equivalent to 0.9 logMAR or 6/48 Snellen). Gabor orientation is random (noise) or tangential to (invisible) concentric circles (signal). The figure in the top left hand corner is the correct answer for this set of form images.



3.6 Ophthalmic assessment

3.6.1 History

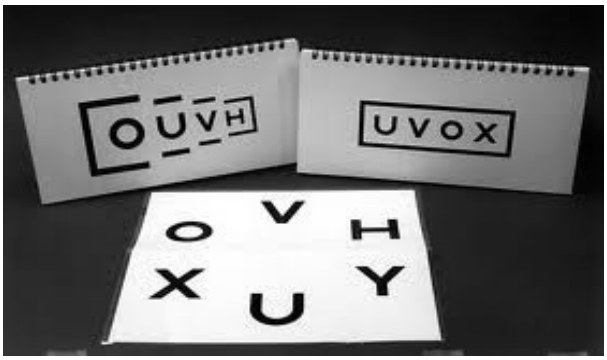
Ophthalmic and family histories are important in assessing a child's vision. For this study, history was elicited from case records and by asking the parents.

3.6.2 Visual acuity

Prematurely born children and control children: Visual acuity - a measure of the ability of the eye to discriminate fine detail – is important as premature birth is associated with poorer acuity thresholds (Sebris et al., 1984, Fledelius, 1981) both for near and for distance (O'Connor et al., 2004).

Visual acuity was measured using the Glasgow acuity cards (Figure 3-7), which are letter charts. The test is performed at 3m distance and incorporates linear progression of letter sizes using log scale. Right eye, left eye and binocular acuity were tested and recorded (McGraw and Winn, 1993). Results were recorded on the score sheet (Appendix 10) with a viewing distance of 3m, right eye, left eye and binocular vision was recorded.

Figure 3-7 Glasgow acuity cards



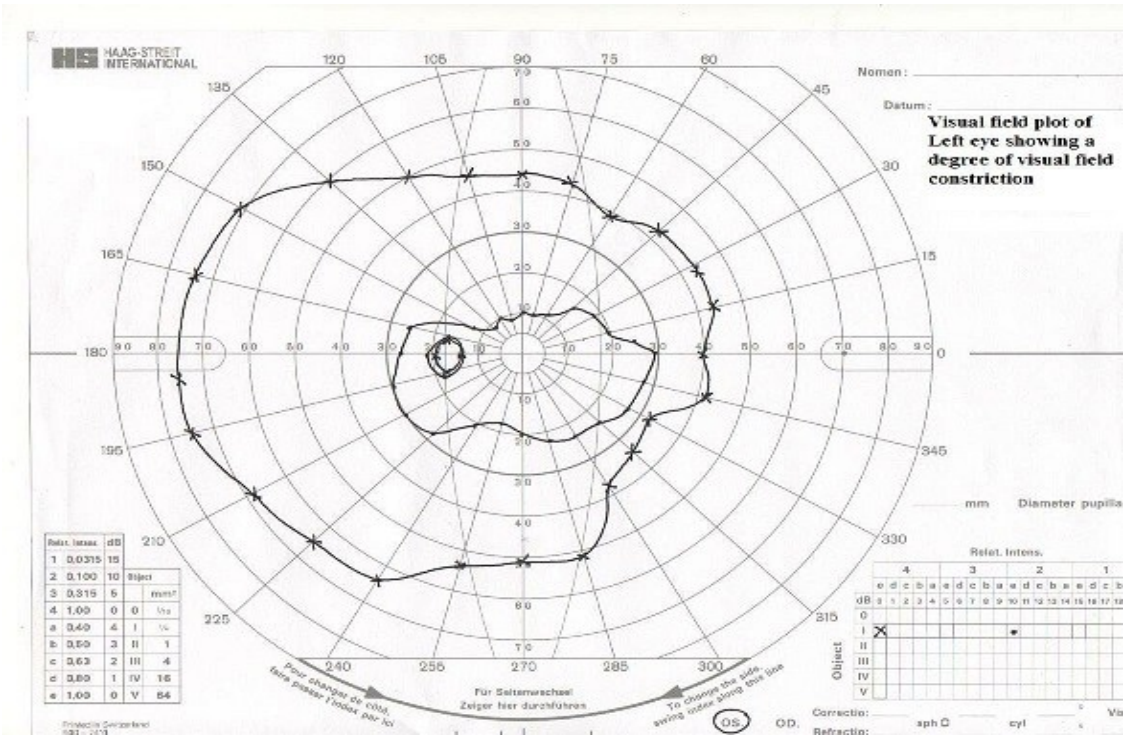
3.6.3 Visual fields

Prematurely born children only: Restricted visual fields are known to be associated with CVI and a history of premature birth. The visual field refers to the total area in which objects can be seen in the peripheral vision while the

subject focuses their eyes on a central point. For this study the Goldmann perimetry (14e target) was used. The Goldmann perimeter is a hollow white spherical bowl positioned a set distance in front of the patient (Figure 3-8). The examiner (Dr K Mitchell) presented a test light of variable size and intensity. The child was asked to press a button when they saw small flashes of light in their peripheral vision. Results were generated from the machine giving a fish map for each eye (Figure 3-9).

Figure 3-8 Goldmann Perimeter

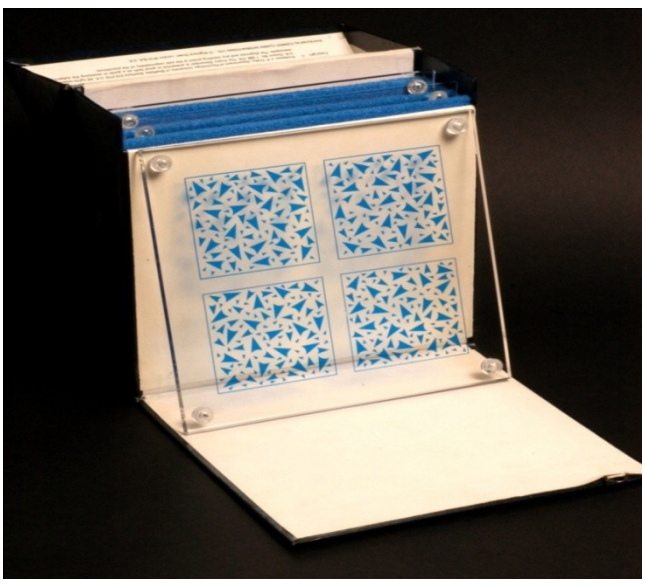
Figure 3-9 Visual field plot of left eye showing a degree of visual field constriction



3.6.4 Stereovision

Prematurely born children and controls: Stereopsis refers to the ability to appreciate depth, due to the lateral displacement of the eyes providing two slightly different views of the same object. Strabismus, reduced acuity and other ophthalmic problems associated with premature birth can reduce stereoacuity: a total absence of stereopsis was found in 12% (Hard et al., 2000) and 17 % (Cooke et al., 2004) of prematurely born infants and abnormal stereopsis was present in 52% (Cooke et al., 2004) and 31% (Hard et al., 2000). All children were tested with the Frisby test (Figure 3-10) where one geometric shape is painted on the far surface of differing thicknesses of perspex plates, creating a range of real depth objects. For stereoacuity assessment the test objective is to find the finest depth discrimination which the child can reliably manage, using the full range of plates (6mm, 3mm and 1.5mm). The objective is to discover if the child can reliably discriminate the target depth using the thickest plate 6mm, the plate is presented several times with target position varied randomly (the thinner the plate and/or the greater the distance, the finer the depth discrimination). A viewing distance of 40cm was used in this study and each plate shown. Subjects with stereopsis usually find the target quickly and confidently. Subjects with defective stereopsis usually make hesitant responses with errors. Stereoacuity best score was recorded on the testing score sheet (Appendix 10).

Figure 3-10 The Frisby stereotest is a test measuring depth perception (in this image the square in the top left hand corner is the one containing the real depth object). Disparity can be altered to find a measure of threshold stereoacuity by changing plate thickness or test distance.



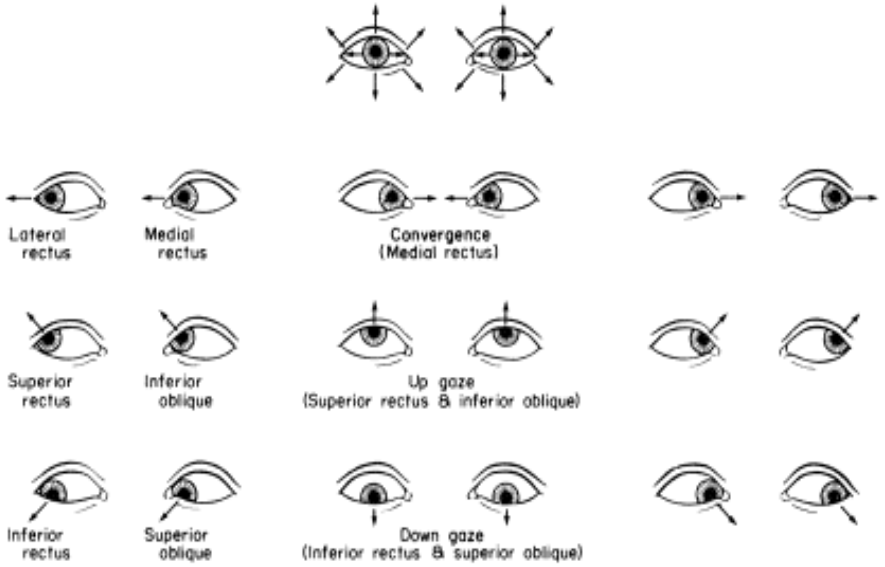
3.6.5 Ocular alignment

Prematurely born children only: Strabismus is a condition in which the eyes are not properly aligned with each other, and can be either a disorder of the brain in co-ordinating the eyes or one of one or more of the relevant eye muscle's power or direction of motion. The increased prevalence of strabismus in prematurely-born infants is well documented: 19.3% compared to just 0.3% of term babies (O'Connor et al., 2002). Subjects were assessed using the cover test where the child focuses on a near, then a distant object while a cover is briefly placed over each eye then removed. The eyes are observed for movement: a strabismic eye will wander inwards or outwards, as it begins to favour its preferred perceptive visual position. The cover test determines the type and amount of ocular deviation. Results were recorded as normal or abnormal with any abnormality noted e.g. exophoria.

3.6.6 Oculomotor function

Prematurely born children only: Assessment of extraocular muscle function and intrinsic ocular muscles were tested for deviations resulting from strabismus, extraocular muscle dysfunction, or palsy (paralysis accompanied by loss of feeling and uncontrolled movements) of the cranial nerves innervating the extraocular muscles. Saccades (quick simultaneous movement of both eyes in the same direction) were assessed by having the subject move his or her eye quickly to a target at the far right, left, top and bottom. Slow tracking, or "pursuits" were assessed by the 'follow my finger' test, in which the examiner's finger traces an imaginary "double-H", which touches upon the eight fields of gaze and tests the extraocular muscles: inferior, superior, lateral and medial rectus muscles as well as the superior and inferior oblique muscles (Figure 3-11), which are designed to stabilise and move the eyes using adduction (the pupil directing toward the nose); abduction (the pupil directed laterally); elevation (the pupil directed up); depression (the pupil directed down); intorsion (the top of the eye moving toward the nose); extorsion (the superior aspect of the eye moving away from the nose). Any abnormal movements were noted and the child asked whether double vision was present.

Figure 3-11 Eye positions for testing extraocular muscle function



3.6.7 Contrast sensitivity

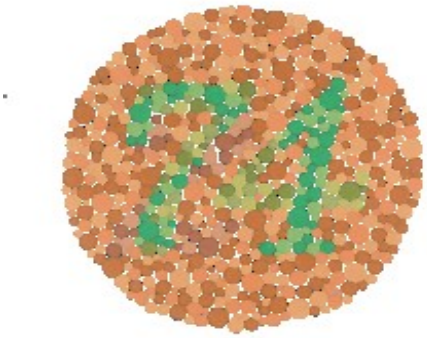
Prematurely born children only: Contrast is defined as the difference in luminance and/or colour that makes an object (or its representation in an image or display) distinguishable. Lower contrast discrimination is seen in prematurely-born born infants than in age-matched children born at term (Abramov et al., 1985, Dowdeswell et al., 1995) and therefore contrast thresholds were assessed using the Peli-Robson contrast sensitivity chart (Figure 3-12) at 1 metre. A score sheet was used to record scores with an underline or circle for each letter read correctly and strike through any letter read incorrectly. The subject's sensitivity is indicated by the faintest triplet for which 2 or 3 letters are named correctly. The log contrast sensitivity for this triplet is given by the number on the scoring pad nearest to the triplet. The number may be to the right or the left of the triplet; the one nearest to the triplet was the one recorded as the Log Contrast sensitivity. Subjects were tested three times; each eye separately and both eyes together and score noted.

Figure 3-12 Peli-Robson contrast sensitivity chart

3.6.8 Colour vision

Prematurely born children only: To allow for any confounding effects of impaired colour vision, where the ability to see colour or perceive colour differences is reduced. Colour vision was assessed using Ishihara plates (Figure 3-13), the City University Colour Vision Test, and the Modified Panel D15 test.

Figure 3-13 Ishihara colour plate: the number "74" should be clearly visible to those with normal colour vision.



The Ishihara test comprises 17 plates. Scores were recorded for each plate, with a score of 10 correct answers out of eleven considered within the normal range. A score of seven or less out of 11 is abnormal, and the subject is considered to have a deficient ability to see colours. Scores were noted for each of the three tests.

3.6.9 Retinoscopy

Prematurely born children only: Retinoscopy provides an objective measure of any refractive error by observing the reflection (reflex) of the retina (farsighted, nearsighted, astigmatism) and the need for glasses. A hand held instrument called a retinoscope projects a beam of light into the eye. The light is moved vertically and horizontally of the eye and distortion indicates the lens strength needed to optimise vision. The ophthalmologist then introduces lenses in front of the eye until the distortion is neutralised. The power of the lens required to neutralise the distortion is the refractive error of the eye and indicates the lens strength needed to optimise vision with spectacles. Cycloplegic eye drops were used to temporarily paralyse or relax the ciliary body, or focusing muscle, of the eyes. Cycoplegic refraction is useful in children as they sometimes subconsciously accommodate their eyes during an eye examination which renders the results invalid.

3.7 Intelligence testing

The prematurely born group underwent the standardised Kaufmann Brief Intelligence Test, subtest of Matrices, Second Edition (KBIT-2) designed for 4-90 year-olds. Subjects were shown on a laptop pictures or abstract designs that follow a pattern but are missing one element, and the participant asked to point to the picture that would complete the pattern. The Matrices subtest includes 46 items. The results were recorded on the test score sheet (Appendix 10), three incorrect consecutive responses ended the test and the score noted. The non-verbal portion assesses problem solving and visual processing. Standardised scores, percentiles and age equivalents were obtained.

3.8 Analysis

CVI questionnaire responses were rated from 1 (never experienced) to 5 (always), with higher scores denoting dysfunction. For initial analytical purposes, scores of 1-3 were deemed negative and 4-5 positive. CVI questionnaire results (proportion of positive:negative responses for each question) were compared between the prematurely born children and the control group in order to investigate which of the 51 questions were able to discriminate between the two groups using Fisher tests. Those questions which were not answered differently (no statistically significant differences between response proportions) by the two groups were excluded from further analysis, creating a reduced questionnaire.

Visual attentional and perceptual test results were analysed using descriptive statistics, scatter plots, and histograms which gave a measure of the location and the spread of data. For each of the tests selected for this thesis, data from the control children were used to construct reference intervals against which to compare data from the prematurely born cohort.

Ophthalmic and IQ findings and summarised histories were analysed with descriptive statistics.

3.8.1 Seeking groups within the prematurely born responders

The subjective perception from the application of earlier versions of the CVI questionnaire used in this study was that parents tended to have either many positive responses, or very few. However, the dataset was highly complex. Cluster analysis was used to seek homogenous subsets of children answering according to similar patterns (CVI questionnaire answers) into a subset (called a cluster) so that observations in the same cluster are similar in response pattern. This process is repeated to join together most – similar clusters. Hierarchical algorithms find successive clusters using previously established clusters.

Cluster analysis was performed on the responses of prematurely born children to questions in the reduced, 18 question questionnaire to find two final clusters with homogeneous answers in terms of the extent of visual difficulties. The cluster analysis used a squared Euclidean distance measure and an agglomerative clustering procedure using Ward linkage. Squared Euclidean

distance was chosen to place the aims of progressively greater weight on objects that are farthest apart (emphasising the difference between "never" and "always" responses). An agglomerative (bottom-up) algorithm was chosen in order to initially treat each element (child) as a separate cluster and merge them into successive larger clusters, thereby making no initial assumptions about their similarity. Ward linkage was chosen as it is a minimum variance algorithm and suitable for use with squared Euclidean distances. This process allowed the creation of two final clusters or sub-groups of prematurely born children.

3.8.2 Further analysis of visual perceptual and attention tests

Between-group (all prematurely-born children, and control children) comparisons were done using T-tests or Mann-Whitney tests as appropriate for the distribution of the data. Having established two prematurely-born sub-groups using cluster analysis, three-way comparisons with the control group were done using ANOVAs, which test the hypothesis that the means of several populations are equal. This method is an extension of the two-sample T-test, specifically for cases where the population variances are assumed to be equal. For non-parametric data, the Kruskal-Wallis one-way analysis of variance by ranks was used to test medians amongst groups. Dunnet's post-hoc comparisons identified any differences between the two clusters (see below) and the control group. An abnormal test result was defined as a score falling outwith the 95th percentile of controls' values.

Since the proportion of infants from multiple births in the study was small, classical statistical methods were used and no adjustments were made for correlations between twins (Shaffler et al., 2009). All analyses for this aspect of the study were performed using Minitab (version 16) with a 5% significance level.

Summary

Chapter 3 has given an overview of the approvals, protocols and methodologies applied to this study. A description was given of the tests carried out for the visual perceptual assessment which were selected to assess presumed dorsal (simultaneous perception, attention and global motion) and ventral stream functions (face recognition and global form). They were selected in an attempt to correlate with the seven underlying aspects of vision explored in the seven

subsections of the CVI questionnaire.

Ophthalmic assessment of visual acuity, stereoacuity and stereopsis was performed on both groups. Additional tests that the study group underwent included visual acuity testing (Keeler crowded and uncrowded logMAR 3 metre test) and bar reading test, contrast sensitivity, stereoacuity, Goldmann perimetry, as well as eye movement assessment and cover tests for manifest or latent strabismus. The study group had an IQ assessment.

Chapter 4 Results

As discussed, although premature birth is recognised as a cause of CVI, the incidence and nature of CVI in prematurely born children is not known. The purpose of this study was to identify whether children born prematurely are at increased risk of CVI. This was achieved by assessing a cohort of 46, prematurely-born children in mainstream primary education and comparing their results with those of 130 control (term-born) children.

4.1 Subjects

Prematurely born children: Eligible children for this study were identified by an experienced consultant paediatrician, Dr B Holland, from the routine follow-up clinic for prematurely born children at the neonatal unit at the Queen Mother's Maternity Hospital, Glasgow, on the basis that they showed no evidence of neurodisability as described in section 3.2.

Families of 71 children were contacted. Forty-six children born between 1996 and 2000 agreed to participate following invitation. The median deprivation score by postal code (DepCat, where 1 is most affluent and 7 is most deprived), (Carstairs and Morris 1991) was 4 for the 46 participants and 5.5 for the 25 non-participants. Thus participants had less social deprivation than non-participants (Mann-Whitney U-test, 95.2% confidence interval of difference 0–3 DepCat points, p=0.03), and the study group was likely to be biased to have less social deprivation than found in the underlying population of eligible children. Non-participation was due to not responding to the invitation (N=18) or poor health (N=7).

Control children: 130 of the 156 control children recruited to Dr. J Calvert's study were recruited to this study. They were born between 1996 and 2002 and included only those control children known to have been born after at least 37 weeks gestation. Control childrens' CVI questionnaire responses and perceptual visual test results were used for comparison. All met the inclusion criteria of having no special needs or reading difficulties (as reported by parents/carers/teachers) and all attended mainstream schools in the same area as the study group.

4.2 Demographic details

Prematurely born study group

The 46 children included eight twin pairs and three triplet groups. Ages ranged from 5.5 to 12.3 years (median 7.9 years). A majority (29/46, 63%) were male. Median birth weight was 1.5 kg (range 0.6 to 2.4 kg). Median gestation was 31.3 weeks (range 24.0 to 34.6 weeks). 61% (N=28) were born by emergency caesarean section, 28% (N=13) normal delivery, with 9% (N=4) by elective caesarean section and one assisted breech delivery.

Control group

The 130 participants were aged 4.7 years to 11.7 years (median age 7.9 years). A majority (73/130, 56%) were female. Median gestation was 40.0 weeks (range 37.0 to 42.0 weeks). Mode of delivery and birth weight were not recorded for the control group (maternal and neonatal notes were not available).

4.3 CVI questionnaire results

CVI questionnaires were completed by parents or carers of all prematurely born and control children. A summary of the responses are presented in Table 4-1, showing the tendency for answers of “often” and “always” for some of the prematurely-born group, and the tendency for answers of “never” or “rarely” for most of the control group.

Table 4-1 Response rates to the 51 questions. Refer to Appendix 1 for details of each question and its subsection. cont: control. prem: prematurely-born.

Question #	Does your child…..	cont -ve	cont +ve	cont % +ve	prem -ve	prem +ve	prem % +ve
1	trip over toys and obstacles on the floor?	127	0	0%	40	6	13%
2	have difficulty walking down stairs?	129	0	0%	41	5	11%
3	trip at the edges of pavements going up?	128	1	1%	44	2	4%
4	trip at the edges of pavements going down?	128	1	1%	44	2	4%
5	appear to 'get stuck' at the top of a slide/ hill?	129	0	0%	46	0	0%
6	look down when crossing floor boundaries e.g. where lino meets carpet?	124	2	2%	44	1	2%
7	leave food on the near or far side of their plate?	125	0	0%	42	3	7%
8	leave food on the right or left side of their plate?	116	0	0%	40	3	7%
9	have difficulty finding the beginning of a line when reading?	126	1	1%	43	3	7%
10	have difficulty finding the next word when reading?	125	0	0%	44	2	4%
11	walk out in front of traffic?	123	0	0%	41	3	7%
12	bump into doorframes or partly open doors?	129	0	0%	41	5	11%
13	miss pictures or words on one side of page?	126	0	0%	44	2	4%
14	have difficulty seeing scenery from a moving vehicle?	129	0	0%	45	1	2%
15	have difficulty seeing things which move quickly, such as small animals?	128	2	2%	42	4	9%
16	avoid watching fast moving TV?	130	0	0%	44	2	4%
17	choose to watch slow moving TV?	124	1	1%	44	1	2%
18	have difficulty catching a ball?	129	0	0%	43	3	7%
19	have difficulty seeing something which is pointed out in the distance?	129	1	1%	38	8	17%
20	have difficulty finding a close friend or relative who is standing in a group?	130	0	0%	40	6	13%
21	have difficulty finding an item in a supermarket , e.g. cereal they want?	130	0	0%	44	2	4%
22	get lost in places where there is a lot to see, e.g. a crowded shop?	129	0	0%	36	9	20%
23	get lost in places which are well known to them?	129	0	0%	45	1	2%
24	have difficulty locating an item of clothing in a pile of clothes?	128	2	2%	35	11	24%
25	have difficulty selecting a chosen toy in a toy box?	130	0	0%	38	8	17%
26	want to sit closer to the television than about 30cm?	126	4	3%	38	8	17%
27	find copying words or drawings time-consuming and difficult?	123	5	4%	41	5	11%
28	hold onto your clothes when walking, tugging down?	126	1	1%	42	4	9%
29	find uneven ground difficult to walk over?	127	1	1%	42	4	9%
30	bump into low furniture such as a coffee table?	127	1	1%	45	1	2%
31	bump into low furniture if it is moved?	125	0	0%	45	1	2%
32	get angry if furniture is moved?	128	0	0%	45	1	2%
33	explore floor boundaries with their foot before crossing?	129	0	0%	46	0	0%
34	find inside floor boundaries difficult to cross?	127	0	0%	44	1	2%
35	reach incorrectly for objects, (beyond or around the object)?	128	0	0%	46	0	0%
36	grasp incorrectly, (miss or knock it over) when picking up an object?	129	0	0%	43	3	7%
37	find it difficult to keep to task for more than 5 minutes?	89	38	30%	40	6	13%
38	find it difficult to get back to what they were doing after being distracted?	100	27	21%	39	7	15%
39	bump into things when walking and having a conversation?	126	3	2%	36	10	22%
40	miss objects which are obvious to you because they are different from their background and seem to 'pop out', e.g. a bright ball in the grass?	128	0	0%	44	2	4%
41	Do rooms with a lot of clutter cause difficult behaviour?	129	0	0%	41	1	2%
42	Do quiet places / open countryside cause difficult behaviour?	129	0	0%			
43	Is behaviour in a busy supermarket or shopping centre difficult?	128	1	1%	44	2	4%
44	react angrily when other restless children cause distraction?	126	2	2%	44	2	4%
45	have difficulty recognising close relatives in real life?	129	0	0%	46	0	0%
46	have difficulty recognising close relatives from photographs?	129	0	0%	46	0	0%
47	mistakenly identify strangers as people known to them?	129	0	0%	45	1	2%
48	have difficulty understanding the meaning of facial expressions?	128	1	1%	45	1	2%
49	have difficulty naming common colours?	129	0	0%	44	2	4%
50	have difficulty naming basic shapes such as squares, triangles and circles?	129	0	0%	46	0	0%
51	have difficulty recognising familiar objects such as the family car?	129	0	0%	46	0	0%

4.3.1 Question modification

It is common practice in designing questionnaires to include a test question by inverting the logical pattern (Streiner and Norman, 2008). This can prevent automatic filling-in of one column. Question 42 'Do quiet places/open countryside cause difficult behaviour?' was included as an inverted test question for control children to interrupt the flow of parents whose children had predominantly positive answers always ticking the right hand box. As expected, the answers were universally 'never' (left hand box), and it was not used for further analysis, having served its purpose of ensuring questions had been read with sufficient care. Two questions elicited high rates of positive responses from parents of control children: questions 37 'Does your child find it difficult to keep to task for more than 5 minutes?' and 38 'Does your child find it difficult to get back to what they were doing after being distracted?' 30% and 21% of parents of control children responded positively to these questions, respectively, as they felt their child struggled to keep to a task or failed to get back to a task after distraction. This demonstrated that being distractible is normal behaviour, and these questions were therefore flagged for exclusion from further refinements of the CVI questionnaire. Results from these three questions (37, 38 and 42) were not included in any analysis.

4.3.2 Comparison of prematurely-born children with controls

For each question, the proportions of prematurely-born children and control children responding positively ("always" or "often") were compared using Fisher's exact test. The purpose of this was to remove those questions where there was no difference in response rate, suggesting that the question was not good at distinguishing between the groups and therefore would not be sensitive for finding aspects of CVI. 18 questions had significantly higher positive response rates on average from prematurely-born children than from control children (Table 4-2). These came from subsections a, b, c, d and e of the CVI questionnaire. All questions from subsections f and g were answered no differently on average by prematurely born and by control children's parents. The higher positive response rates for prematurely born children than for control children suggest more problems with everyday visual tasks.

Table 4-2 Comparison of response rates to CVI questionnaire (Appendix 1). The table shows the 18 questions answered significantly more positively by prematurely born children at the top unshaded section (in questionnaire subsection and number order). ***p<0.0005, **p<0.005, *p<0.05, NS p>0.05. The grey shaded section shows questions with no statistical significance.

Question #	aspect of CVI (see methods)	% of controls (N=130) responding "often" or "always"	% of prematurely born children (N=46) responding "often" or "always"	significance of difference from Fisher exact test
1	a	0%	13%	***
2		0%	11%	**
7		0%	7%	*
8		0%	7%	*
11		0%	7%	*
12		0%	11%	**
15	b	2%	9%	*
18		0%	7%	*
19	c	1%	17%	***
20		0%	13%	***
22		0%	20%	***
24		2%	24%	***
25		0%	17%	***
26		3%	17%	**
28	d	1%	9%	*
29		1%	9%	*
36		0%	7%	*
39	e	2%	22%	***
3	a	1%	4%	NS
4		1%	4%	NS
5		0%	0%	NS
6		2%	2%	NS
9		1%	7%	NS
10		0%	4%	NS
13		0%	4%	NS
14	b	0%	2%	NS
16		0%	4%	NS
17		1%	2%	NS
21	c	0%	4%	NS
23		0%	2%	NS
27		4%	11%	NS
30	d	1%	2%	NS
31		0%	2%	NS
32		0%	2%	NS
33		0%	0%	NS
34		0%	2%	NS
35		0%	0%	NS
40	e	0%	4%	NS
41		0%	2%	NS
43		1%	4%	NS
44	f	2%	4%	NS
45		0%	0%	NS
46		0%	0%	NS
47		0%	2%	NS
48	g	1%	2%	NS
49		0%	4%	NS
50		0%	0%	NS
51		0%	0%	NS

As a result of the Fisher exact test analysis of all questions, 18 questions were identified which distinguished the prematurely-born and the control children (Table 4-3). In order to maximise the sensitivity of the questionnaire to any manifested visual difficulties experienced by the prematurely born group, only these 18 questions were used in subsequent analysis of the questionnaire responses.

Table 4-3 Reduced 18 question questionnaire.

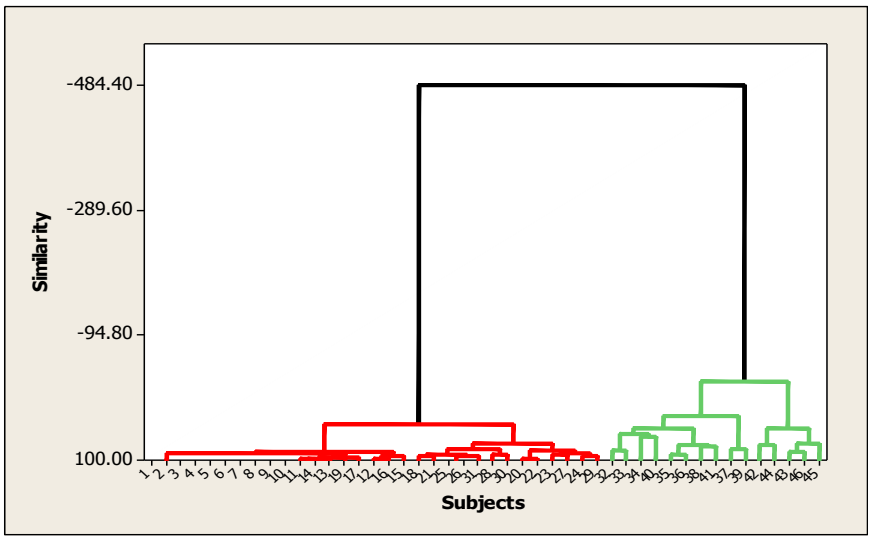
Subsection A: Questions seeking evidence of visual field impairment or impaired visual attention on one or other side. Does your child ……
trip over toys and obstacles on the floor?
have difficulty walking downstairs?
leave food on the near or far side of their plate?
leave food on the right or left side of their plate?
walk out in front of traffic?
bump into doorframes or partly open doors?
have difficulty seeing things which are moving quickly, such as small animals?
have difficulty catching a ball?
Subsection B: Questions seeking evidence of difficulty handling complexity of a visual scene. Does your child ……
have difficulty seeing something which is pointed out in the distance?
have difficulty finding a close friend or relative who is standing in a group?
get lost in places where there is a lot to see, e.g. a crowded shop?
have difficulty locating an item of clothing in a pile of clothes?
have difficulty selecting a chosen toy in a toy box?
want to sit closer to the television than about 30cm?
Subsection C: Questions seeking evidence of impairment of visually guided movement of the body and further evidence of visual field impairment. Does your child ……
hold onto your clothes, tugging down, when walking?
find uneven ground difficult to walk over?
grasp incorrectly, that is do they miss or knock the object over, when picking it up?
Subsection D: Questions seeking evidence of impaired visual attention. Does your child
bump into things when walking and having a conversation?

4.3.3 Cluster analysis of prematurely-born children

Inspection of responses for the prematurely born children to this reduced, 18-question questionnaire revealed two response patterns: those who frequently responded ‘often’ or ‘always’, and those who seldom or never did so, suggesting the presence of two groups within the prematurely born cohort, one experiencing some difficulties with everyday visual tasks and another unaffected group.

To assess whether two homogenous subgroups of prematurely born children did exist, based on the detail of the questionnaire responses, cluster analysis was performed, seeking two clusters in the final partition. The two final clusters (labelled A and B) contain children whose questionnaire responses were similar. Cluster A (N=15) children’s responses indicated visual difficulties and cluster B (N=31) children manifested few if any difficulties. Statistical output of the cluster analysis is given in Appendix 11. A dendogram of the agglomerative clustering process is shown in Figure 4-1: this can be reads upwards, with most similar children (in terms of questionnaire responses) joined in the first step of the hierarchy to form multiple small clusters; in the next and subsequent stages, the most similar clusters are again agglomerated.

Figure 4-1 Dendogram of clustering of prematurely born children's questionnaire responses (N=46) illustrating the successive clustering of observations using Ward linkage and squared Euclidean distance: the green on the right hand side representing final cluster A (N=15) and red on the left of the figure illustrating final cluster B (N=31). The x-axis shows individual subjects and the y-axis the similarity between clusters based on the squared Euclidean distance between clusters at each level of the heirarchy.



These findings suggest that, based on patterns of responses to 18 questions in the CVI questionnaire, 15/46 (33%, 95% CI 21–47%) of the prematurely born children had behaviours corresponding to the everyday visual difficulties observed in CVI.

Using the 1–5 scoring system (1 for "never", 5 for "always") for each question in the questionnaire, a reduced (18-question) questionnaire total score of 37 or higher was sensitive (100%; 95% confidence interval 75–100%) and specific (100%; 95% confidence interval 86–100%) for membership of cluster A.

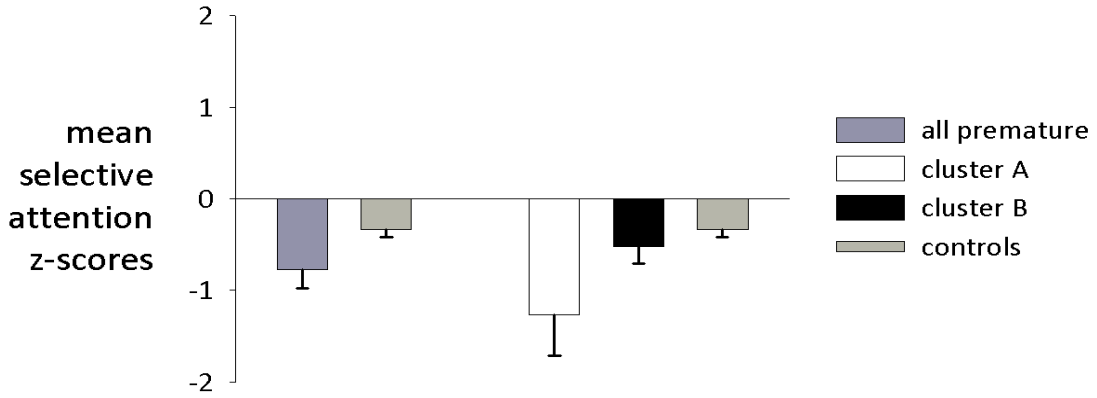
4.4 Visual attention testing

For all four visual attention tests – selective attention, attentional control/switching, sustained attention and sustained-divided attention – prematurely born children had significantly poorer scores than controls (Figures 4-2 to 4-6). Table 4-4 summarises all the results (page 81).

4.4.1 TEA-Ch: Selective attention: ("Sky Search")

The prematurely born group (N=46) had a mean selective attention z score of -0.78 compared to a mean z score of -0.33 for the control group (N=130). Three-way comparisons of scores for cluster A, cluster B and control children revealed significant group differences for selective attention (1-way ANOVA, p=0.023). Dunnett's post-hoc comparison showed cluster A performed significantly worse than controls (-1.27 vs.-0.33). Cluster B children performed slightly worse than controls (-0.52 vs. -0.33) (Figure 4-2).

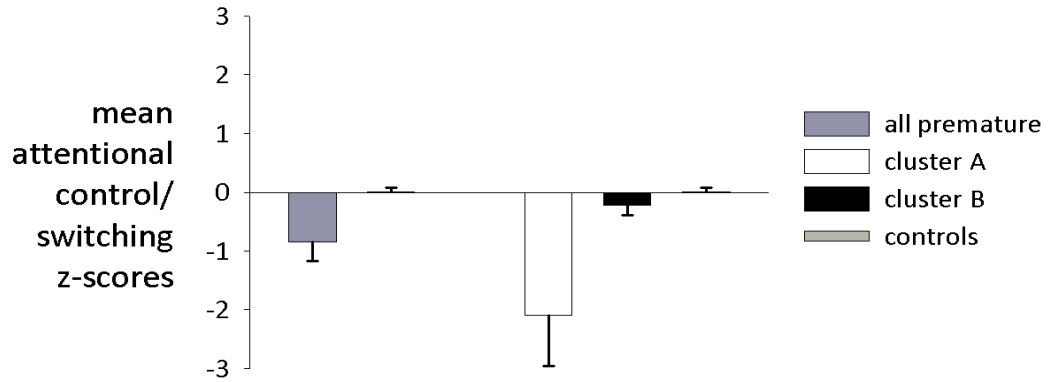
Figure 4-2 Results of the selective attention task "Sky Search". On the left, the whole prematurely born group is compared with controls; on the right, the prematurely born group is separated into cluster A (white) and cluster B (black), and compared with controls as before. Error bars ± standard error of the mean.



4.4.2 TEA-Ch Attentional control/switching: ("Opposite Worlds")

The prematurely born group (N=46) had a mean attentional control/switching z score of -0.85, compared to a mean z score of 0.003 for the control group (N=130); the prematurely born group performed worse than the control group (Table 4-4). Three-way comparisons of scores for cluster A, cluster B and control children revealed significant group differences (1-way ANOVA, $p<0.0005$). Dunnett's post-hoc comparison showed cluster A performed significantly worse than controls (-2.10 vs. 0.003), whereas cluster B performed no worse than controls (-0.22 vs. 0.003) (Figure 4-3).

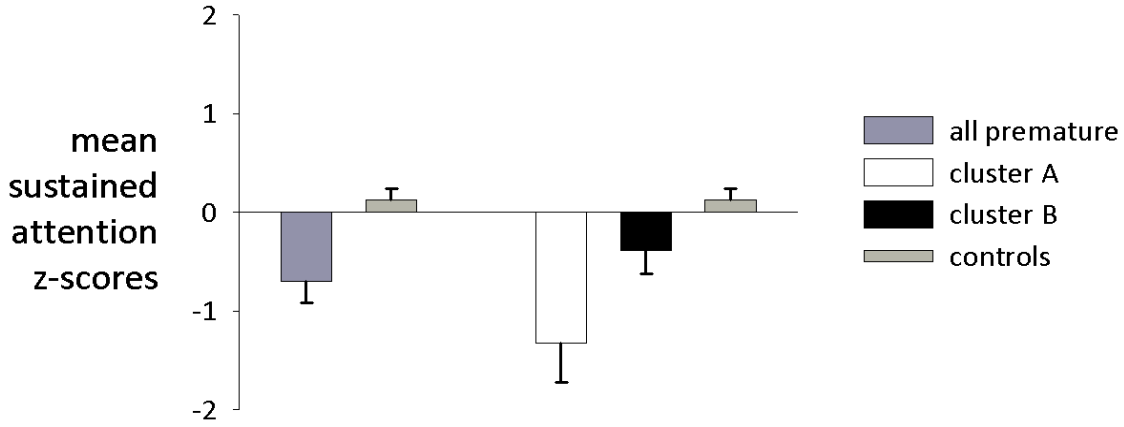
Figure 4-3 Results of attentional control/switching task. On the left, the whole prematurely born group is compared with controls; on the right, the prematurely born group is separated into cluster A (white) and cluster B (black), and compared with controls as before. Error bars ± standard error of the mean.



4.4.3 Sustained attention ("Score!")

The prematurely born group (N=46) had a worse mean sustained attentional z score of -0.70, compared to a mean z score of 0.13 for the control group (N=130). Three-way comparisons of scores for cluster A, cluster B and control children revealed significant group differences (1-way ANOVA, $p<0.0005$), and Dunnett's post-hoc comparison showed cluster A performed significantly worse than controls (-1.33 vs. 0.13), whereas cluster B performed no worse than controls (-0.39 vs. 0.13) (Figure 4-4).

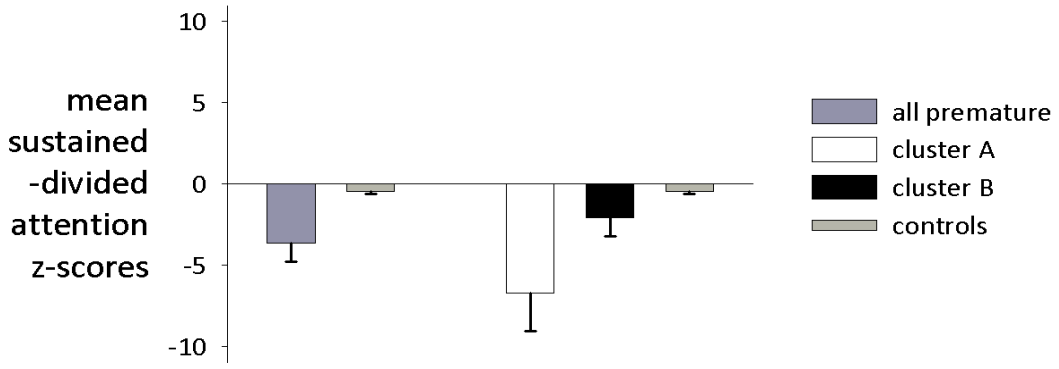
Figure 4-4 The results of the sustained attention task. On the left, the whole prematurely born group is compared with controls; on the right, the prematurely born group is separated into cluster A (white) and cluster B (black), and compared with controls as before. Error bars ± standard error of the mean.



4.4.4 Sustained/divided attention ("Sky Search DT")

The prematurely born group (N=46) had a mean sustained/divided z score of -3.65, compared to a mean z score of -0.46 for the control group (N=130). Three-way comparisons of scores for cluster A, cluster B and control children revealed significant group differences (1-way ANOVA $p<0.0005$). Dunnett's post-hoc comparison showed cluster A performed significantly worse than controls (-6.73 vs. -0.46), whereas cluster B performed no worse than controls (-2.10 vs. -0.46) (Figure 4-5).

Figure 4-5 Mean data and statistical results of mean sustained/divided attention. On the left, the whole prematurely born group is compared with controls; on the right, the prematurely born group is separated into cluster A (white) and cluster B (black), and compared with controls as before. Error bars ± standard error of the mean.



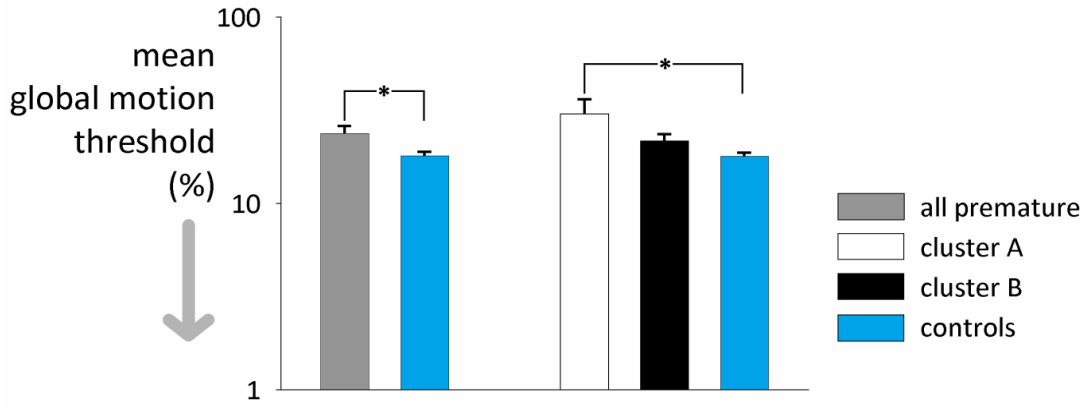
4.5 Visual perception tests

For all four visual perception tests (global motion, visual closure, facial recognition, global form) (Section 3.5.2 – 3.5.4), prematurely born children had poorer scores than controls; differences reached statistical significance for all tests except the visual closure test. An abnormal test result was defined as a score falling outwith the 95th percentile for controls (≤7 for visual closure standard score; ≥27% for global form and ≥37% for global motion thresholds), or a T-score <30, or a z-score <-2.

4.5.1 Global motion

Global motion as described in section 3.5.2 was used to assess perception of movement and visually guided movement. The average thresholds for the prematurely born group (N=46) was 23.8%, significantly worse than for the controls (N=130,18%), two sample t-test result p=0.001 (Table 4-4). Three-way comparison of cluster A, cluster B, and controls showed a significant difference (1-way ANOVA, p=0.001). Those children unable to complete the global motion test (N=2) were in cluster A. Cluster B children performed no differently to controls (Figure 4-6).

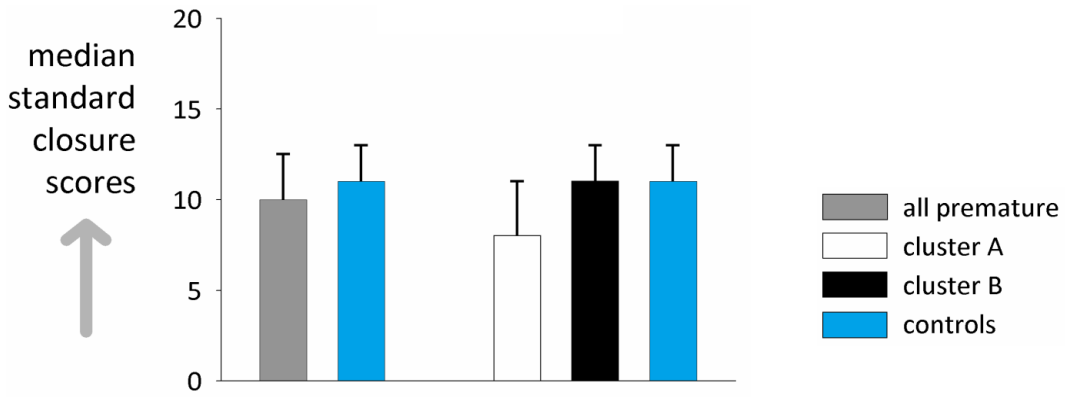
Figure 4-6 Results of the global motion test. The grey arrow indicates the direction of better performance. First two columns: entire prematurely born group and control group. Last three columns: cluster A (white), cluster B (black) and controls as before. Error bars are ± standard error of the mean for the global motion.



4.5.2 Visual closure (DTPV)

The DTPV subtest closure was applied as described in Section 3.5.3. Prematurely born children (N=46) had a median standard closure score of 10 closure (range 3-16) compared with 11 (range 2-16) for control children. These scores were not significantly different (Mann-Whitney U test, p=0.052). Three-way comparisons of scores for cluster A (N=15), cluster B (N=31) and control children (N=130) did not identify any significant group differences for the test of visual closure (Kruskal-Wallis, p=0.079) (Figure 4-7).

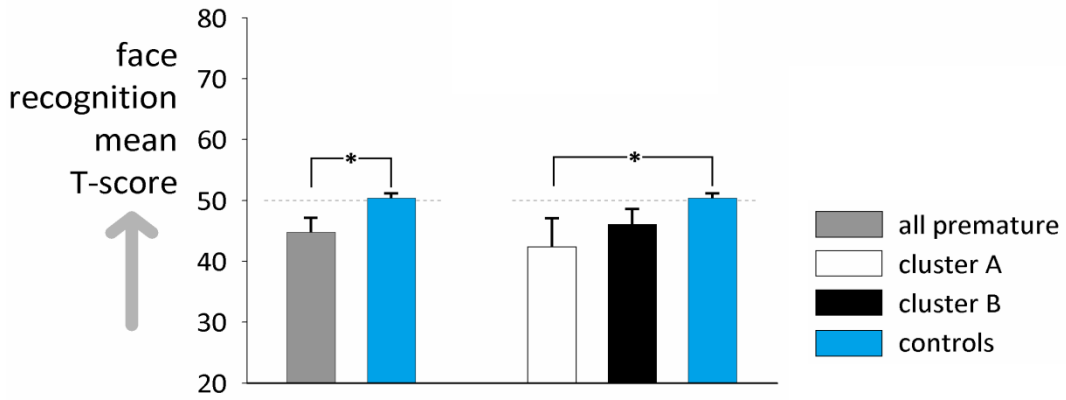
Figure 4-7 Results of the DTPV subtest closure. The grey arrow indicates the direction of better performance. First two columns: entire prematurely born group and control group. Last three columns: cluster A (white), cluster B (black) and controls. Error bars are ± median absolute deviation for the closure test.



4.5.3 Stirling facial recognition (SFR) test

The SFR test as described in section 3.5.4.1 was used to assess facial recognition. The T-score for the prematurely born group (N=46) was 44.8 compared to 50.3 for the controls (Table 4-4). Three-way comparison of cluster A, cluster B, and controls showed a significant difference (1-way ANOVA, p=0.004). Cluster A children performed significantly worse than control children; (Figure 4-8) 42.3 versus 50.3 for the controls. Cluster B performed no differently to controls.

Figure 4-8 Results of the Stirling face recognition test. The grey arrow indicates the direction of better performance. First two columns: entire prematurely born group and control group. Last three columns: cluster A (white), cluster B (black) and controls as before. Error bars are ± standard error of the mean.



4.5.4 Global form

Global form as described in section 3.5.4.2 was used to assess the children's ability to integrate position and orientation signals from elements (oriented Gabors) distributed within a stimulus array. The average thresholds for the prematurely born group (N=46) was 16.8%, poorer than that of the controls (N=130) which was 13.2%, two sample t-test, p=0.008 (Table 4-4). Three-way comparison of cluster A, cluster B, and controls showed a significant difference (1-way ANOVA, p<0.001). Cluster A children performed significantly worse than control children, but cluster B children performed no differently to controls (Dunnett's post-hoc comparisons). Cluster B children performed no differently to controls (Figure 4-9).

Figure 4-9 Results of the global form test. The grey arrow indicates the direction of better performance. First two columns: entire prematurely born group and control group. Last three columns cluster A (white), cluster B (black) and controls as before. Error bars are ± standard error of the mean.

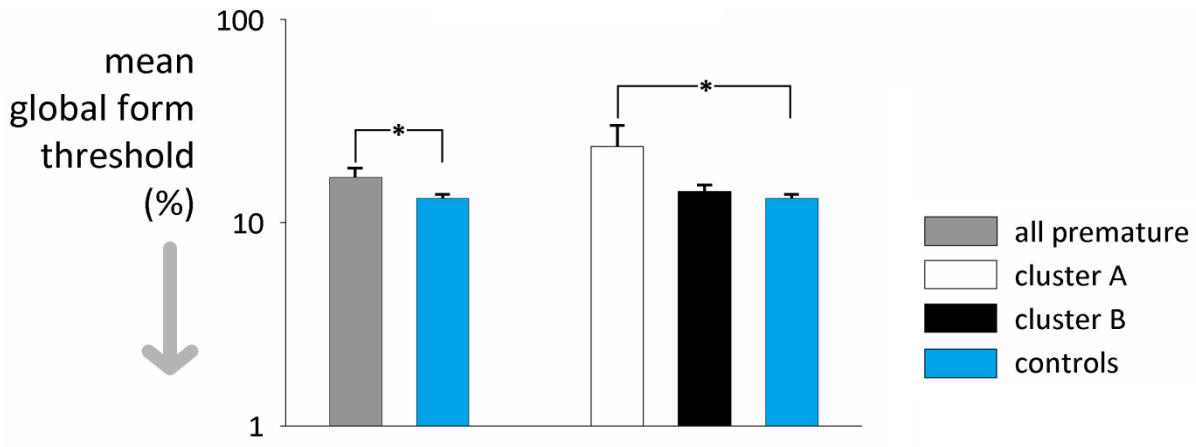


Table 4-4 Summary of findings of visual attention and perception tests.

		prematurely born children			control children	prematurely born children poorer than controls?	cluster A poorer than controls?	cluster B poorer than controls?
		all (N=46)	cluster A (N=15)	cluster B (N=31)				
visual perception tests	visual closure standard	10 (5)	8 (9)	11 (4)	11 (4)	no (p=0.07)	no	no
	global form threshold	16.8 (2.4)%	23.6 (9.4)%	14.2 (1.3)%	13.2 (0.7)%	yes (p=0.03)	yes	no
	global motion threshold (mean; SE)	23.8 (2.1)%	30.1 (6.0)%	21.3 (2.0)%	18.0 (0.8)%	yes (p=0.004)	yes	no
	face processing T-score (mean, SE)	44.8 (2.3)	42.3 (4.7)	46.0 (2.6)	50.3 (0.8)	yes (p=0.03)	yes	no
visual attention test (z-scores)	selective attention (mean, SE)	-0.78 (0.20)	-1.27 (0.45)	-0.52 (0.19)	-0.33 (0.09)	yes (p=0.023)	yes	no
	attentional control / switching (mean, SE)	-0.85 (0.33)	-2.10 (0.87)	-0.22 (0.17)	0.003 (0.07)	yes (p=0.016)	yes	no
	sustained attention (mean, SE)	-0.70 (0.22)	-1.33 (0.40)	-0.39 (0.24)	0.13 (0.11)	yes (p=0.001)	yes	no
	sustained-divided attention (mean, SE)	-3.65 (1.13)	-6.73 (2.36)	-2.10 (1.14)	-0.46 (0.17)	yes (p=0.008)	yes	no

In summary, for all four visual perception tests – visual closure, global form, global motion and face recognition-prematurely born children had poorer scores than controls. In every test it was cluster A children who created the differences, not cluster B.

4.6 Ophthalmic assessment of visual function

Visual function testing, as described in section 3.6, was only carried out on the prematurely–born cohort (N=46). Comparing the prevalence of visual function abnormalities between the two clusters of prematurely born children identified abnormalities of stereoacuity, contrast sensitivity and eye movements which were more frequent in cluster A (Table 4-5). Such differences were not identified for visual fields, visual acuity or strabismus. The control cohort did not have full visual assessment therefore comparison is not possible.

Table 4-5 Comparison of prevalence of visual function abnormalities between the two clusters of prematurely born children. Objective decision limits for abnormality were: stereoacuity ≥75', contrast sensitivity <1.75%, acuity >0.1 logMAR. Shaded grey areas are those values showing significant changes.

	proportions with abnormal findings		
	cluster A (N=15)	cluster B (N=31)	p-value, Fisher's exact test
stereoacuity	5/14	4/27	0.013
contrast sensitivity	4/11	1/27	0.019
eye movements	3/11	0/27	0.02
near acuity	2/13	0/27	0.12
distance acuity (uncrowded)	3/13	3/27	0.4
distance acuity (crowded)	3/13	3/27	0.4
fields	2/10	2/23	0.6
strabismus	2/9	2/26	0.6

4.6.1 Visual acuity

Median distance acuity was 0.000 logMAR (crowded) and -0.075 logMAR (uncrowded) for the premature children (N=40) in the present study. Nineteen had crowded acuities worse than 0.000 (range 0.025 to 0.700), and 12 had uncrowded acuity worse than 0.000 (range 0.025 to 0.700). 14/15 of the children with CVI were tested: they had worse distance acuity by one letter and four

letters, crowded and uncrowded respectively, than those preterm children without CVI. Near acuity was N5 (0.2 logMAR) for 37/40 of the preterm children tested; one was N6 (0.3 logMAR) and two were N24 (0.9 logMAR). All three of the preterm children with poorer near acuity were in cluster A.

The VA of 73 prematurely born and 73 full-term born infants were tested at 6 months of age by the Teller Acuity Card procedure (standard tests for visual acuity depend on verbal responses from the test subjects – the Teller Acuity Cards offer an easy method for screening non-verbal subjects especially infants and children)(Teller, 1979). Mean GA of the premature infants was 33 weeks as compared with 39.9 weeks in full-term infants. The mean birth weights of the 2 groups were 1,906 +/- 412 and 3.244 +/-420g respectively. Impaired binocular visual acuity was found in 53.4% of the premature infants, but in only 11% of the full-term infants ($p < 0.0001$). Impaired monocular visual acuity was found in 13.7% of the premature infants as compared with 2.7% of the full-term infants. Both the study of Spierer et al, (2004) and the present study indicate that both monocular and binocular visual acuities are poorer in prematurely born infants than in full-term infants at the same chronological age.

4.6.2 Colour vision

Ishihara Plates: 9/33 children had abnormal Ishihara scores, (not done on 7 children; one child could not do the test); 2/33 had abnormal City Universal scores (not done on 8 children; 2 could not do the test; and 17/35 children had abnormal panel D15 scores (not done on 11; one child could not do the test). On the modified Panel D15 test, 51% (18/35) children had abnormal results. Of these 18, 61% (8/13) cluster A and 45% (10/22) B, children had abnormal results.

4.6.3 Visual fields

Visual field analysis to the 14e Goldmann isoptre was feasible for 24 of the children tested, with three having to be abandoned due to poor concentration. Of the remaining 21 infants 20 had normal results with one subject being borderline. Of the 22 children not tested 19 of these were due to poor concentration and the remaining two due to time constraints.

4.6.4 Refraction

Refraction was performed on 26/46 children; 10/26 had no refractive error and 16/26 required refractive correction.

4.7 Intelligence testing

The prematurely born children had lower than normal non-verbal IQs (Table 4-6). Standard scores ranged from 59 to 118 (median 85). Median IQ standard scores for cluster A (84.5; range 59 to 114), and cluster B (86.5; range 64 to 118) were not significantly different (Mann-Whitney U-test, p=0.75).

Table 4-6 KBIT-2 nonverbal standardised scores (this test was not done on two children due to time restraints).

Descriptive category	Total N=44	cluster A N=14	cluster B N=30
Upper extreme (>130)	0	0	0
Above average (116-130)	1	0	1
Average (85-115)	24	7	17
Below average (70-84)	16	6	10
Lower extreme (<70)	3	1	2

4.8 Birth parameters

Birth parameters show cluster A children to have lower birth weight, shorter gestation, poorer Apgar scores and greater proportions of males and emergency section deliveries (Table 4-6). Median Apgar score was 9 at one minute (range 1-9), median score at 5 minutes was 9 (range 4-10). However, there was no statistically significant differences between cluster A and B children in birth weight (p = 0.09), gestation (p = 0.12), or Apgar scores (p = 0.4, p = 1.0).

Table 4-7 Comparison of birth parameters for prematurely born children by cluster A (N=15) and cluster B (N=31)

	birthweight (g: mean, sd)	gestation (weeks: mean, sd)	Apgar @ 1 min (median; IQR)	Apgar @ 5 mins (median; IQR)	proportion of males	proportion of emergency sections
cluster A	1368 (570)	29.9 (3.1)	6 (5.5)	9 (0)	11/15 (73%)	11/15 (73%)
cluster B	1664 (432)	31.4 (2.5)	8 (4)	9 (1)	18/31 (58%)	17/31 (55%)

4.9 The clinical picture

A descriptive set of information was condensed from the responses of the 15 cluster A children to the entire CVI questionnaire (48 questions). This illustrates the presence or absence of visual difficulties by subsection experienced by cluster A children (Table 4-8). The aspect common to all 15 children is difficulty handling complex visual scenes; in other words, all 15 cluster A children had positive ("always" or "often" responses to at least one of the questions in subsection C.

Table 4-8 Illustration of which of the seven aspects of CVI (as identified by the CVI questionnaire) showing deficits for the fifteen prematurely born children identified by cluster analysis (cluster A).

	a) visual field impairment or impaired visual attention to one side	b) impaired perception of movement	c) difficulty with handling complexity of a visual scene	d) impairment of visually guided movement of the body	e) impaired visual attention	f) difficulties associated with a crowded environment	g) difficulties with recognition and navigation
1	YES		YES				
2	YES	YES	YES	YES	YES		
3		YES	YES		YES	YES	YES
4	YES		YES	YES		YES	
5	YES	YES	YES	YES			YES
6	YES		YES	YES	YES	YES	
7			YES				
8	YES		YES		YES		
9	YES	YES	YES	YES	YES		
10	YES	YES	YES	YES	YES		YES
11	YES	YES	YES	YES	YES		
12	YES		YES	YES	YES		
13		YES	YES	YES	YES		
14	YES		YES				
15	YES		YES	YES	YES		

Summary

Eighteen questions of the CVI inventory were answered more positively by prematurely born children than by control children.

Fifteen of the 46 (33%) of the prematurely born children '(cluster A)'- revealed behaviours corresponding with CVI on cluster analysis of these 18 questions of the CVI questionnaire. The whole prematurely born group performed worse than controls on all visual perception tests and all four visual attention tests. Children in cluster A were responsible for this effect, performing worse than controls on all visual perception and attention tests except visual closure, while cluster B prematurely born performed no differently from controls.

Cluster A children were more likely to be male, delivered by emergency section, have abnormal stereoacuity, contrast sensitivity or eye movements. However, cluster A and B children did not differ on average birth parameters, IQ or visual functions such as acuity or field constriction.

Difficulty with complex visual scenes was common to all cluster A children.

Chapter 5 Discussion

Introduction

The 20th century has seen a gradual progression of understanding of the human visual system. Its disorders as a sequel to brain damage in adults has confirmed that many of the signs and symptoms seen in children today have been reported in adults as far back as the 1900s (Holmes, 1918). Specific visual difficulties are now recognised to affect children with damage to the brain (Bracewell and Marlow, 2002).

Prematurity is a recognised cause of CVI in children but to date the incidence and nature of CVI in prematurely born children have not been studied in detail. This study aimed to identify whether children born prematurely are at increased risk of CVI by recording the incidence and nature of CVI in children born prematurely (<37 weeks) and comparing this to a full-term cohort.

5.1 CVI in prematurely born children:

CVI is the commonest cause of impaired vision in children in the developed world. CVI has frequently been recognised in children born prematurely, possibly often due to white-matter pathology which may, or may not, be evident on MRI scan. As discussed in section 2.1, prematurity remains the principal cause of infant mortality and morbidity in industrialised countries (Wen et al., 2004). But does this tell the full story for prematurely born children? Comparison of visually associated problems in children born prematurely is hindered due to the variability of techniques used to assess and report, for example, different visual acuity tests or contrast sensitivity tests; sub-groups such as prematurity, low birth weight, or gestational age as well and the inclusion or exclusion of major deficits.

In the present study the premature cohort (N=46) were separated using cluster analysis into cluster A and cluster B based on responses to the CVI questionnaire. Those in cluster A (identified as having CVI) were born 1½ weeks earlier, had poorer Apgar scores and a greater proportion of males and more emergency caesarean section deliveries on average than cluster B children. Difficulties with visual complexity were described in all 15 children in Cluster A; impaired visual

fields or impaired attention in 12 and impaired visually-guided movement in 10. This pattern is similar to 'dorsal stream dysfunction' (section 2.3.5). Such difficulties are associated with premature birth, and may partly explain under-achievement in reading and mathematics (Williams et al., 2011). In prematurely born children with occipital brain MRI imaging anomalies, and spastic diplegia, very similar patterns of perceptual and visuomotor dysfunction are commonly identified (Fazzi et al., 2004).

Prematurity is known to give rise both to ophthalmological disorders e.g. strabismus, refractive error and retinopathy of prematurity; (O'Connor et al., 2004) and to CVI due to brain damage, for example PVL. Other visual pathways may be affected in preterm infants with cerebral damage e.g. LGN, calcarine cortex and visual associative areas giving rise to reduced visual acuity, restricted visual fields and ocular incoordination to complex visual cognitive disorders (Fazzi et al., 2004). Jacobson et al. (1998a) investigated a cohort of prematurely born infants to identify the causes of VI in a population similar to the present study of visually impaired children prematurely born. The sample size was smaller than the present study (N=18 versus N=46) with a lower gestational age (median of 29 weeks versus 31 weeks). Lesions of the posterior visual pathways accounted for 16 of the 18 cases reported by Jacobson et al. Ten of the 16 cases had confirmed PVL as a cause, 2 of the 16 prenatal infection, one case of infection and one case of optic nerve hypoplasia (Jacobson et al., 1998a). One of the main differences between Jacobson's study and the present study was the inclusion criteria. The inclusion criteria set by Jacobson et al. included a brain lesion caused by perinatal hypoxic–ischaemic events in the immature brain at 24-34 weeks gestation, has a typical anatomical pattern with periventricular leucomalacia (PVL) confirmed by Jacobson's study but none of the current study cohort had a confirmed diagnosis of PVL. All children in Jacobson's study had strabismus (N=18), with ten being exotropic and eight esotropic. In the current study only four children had strabismus, two in each cluster. VI due to reduced acuity as measured by linear optotype was diagnosed in 15 of the 18 children in Jacobson's study with three not able to be evaluated due to abnormal fixation with roving eyes. In conclusion Jacobson et al. (1998b) noted that brain damage should be suspected in prematurely born children who present with either signs of fixation difficulties, strabismus or nystagmus.

The only published study to date using a questionnaire to aid identification of CVI is Ortibus et al. (2012) who investigated the screening utility of a questionnaire for CVI by correlating the questionnaire with diagnostic tools. They describe CVI resulting from impaired processing of visual information on the presence of a (nearly) normal intact ophthalmological system. The classical model of cerebral visual problems (dorsal and ventral stream) as presented in this current study is also described, taking the model a stage further by emphasising that additional problems with sustained eye contact, odd behaviour in crowded environments and decreased sustained visual attention do not fit neatly into the dorsal/ventral dichotomy and needs to be elicited by history taking in accordance with previous published studies investigating CVI (, Dutton, 2003a, Fazzi, 2004, Macintyre-Beon, 2012).

The questionnaire developed by Orbitus et al. (2012) comprised 46 items exploring different characteristics of CVI. The 46-item questionnaire included 46 closed ended items which were selected from existing questionnaires used by home visiting teams in Flanders, the visual skills inventory developed by Dutton et al. (2001) and a literature review of features of CVI in children (Dutton, 2001, Fazzi, 2004, Edmond, 2006, Carlon S, et al., 2010). The questionnaire developed is similar to that used in the present study, having six sub-sections while the present study had seven sub-sections covering similar features. Ortibus et al. (2012) added a sub-section of visual attitude, and a sub-section for dorsal, with another for ventral questions in two separate categories (the present study subdivided groups to characteristics of the various symptoms often presented by children with CVI). Of the 91 children recruited to their study 49% were diagnosed as having CVI. This is higher than the present study and several factors account for the higher rate in Ortibus' study (49 vs 33%). They recruited children referred to their tertiary referral centre for children with visual perceptual problems, and consecutively recruited a cohort of children following referral to the CVI clinic. Of the 91 children recruited, 45% (41/91) had cerebral palsy, 12% (11/91) autism spectrum disorder and 3% (3/91) developmental dyspraxia, whereas the current study comprised children without any motor, neurodisability or learning difficulties and were attending mainstream education. Gestational age of the subjects recruited to that study had a mean age of 37 weeks (range 24-41 weeks) compared with those in the present study who had a median GA of

31.3 weeks (range 24.0–34.6 weeks). Sixty-four percent were males in Orbitus' study, similar to the 63% males in the present study.

The sub-section "visual attention" in Orbitus' study was scored positive most frequently, with 25% of children having attentional problems. This pattern was similar to the present study where the cluster A children performed significantly worse for all attentional tests. Orbitus et al. (2012) had 36% (33/91) subjects with strabismus and 13% (12/91) with nystagmus, the current study recorded 11% (4/35) with strabismus and no children were identified as having nystagmus. Visual field loss was identified in 9% of children studied by Orbitus and 12% in the current study . However, these figures cannot be compared as it is not known how many of the 91 children actually had visual fields measured using the Goldman isoptre. In accordance with the present study, Orbitus et al. (2012) concluded that a CVI questionnaire was a viable tool with the potential of being implemented as part of a routine screening procedure for CVI (Orbitus, 2011).

5.2 Visual attention testing

For all four visual attention tests, prematurely born children had significantly poorer scores than controls. Three-way comparisons of scores for cluster A, cluster B and control children revealed significant group differences for selective attention, attentional control/switching, sustained attention and sustained-divided attention ($p<0.008$, $p<0.0005$, $p<0.0005$ and $p< 0.0005$ respectively). *Post hoc* comparisons showed cluster A children performed significantly worse than control children for all tests, whereas cluster B children performed no worse than controls. All the children who were unable to complete the selective attention test (N=3) and the attentional control / switching test (N=1) were in cluster A: four cluster A children and three cluster B children were unable to complete the sustained-divided attention test. Cluster A children also scored significantly worse on all the attention tasks than those in cluster B, perhaps reflecting posterior parietal dysfunction impairing attention associated with superior parietal lobe dysfunction in prematurely born children via simultanagnosia and in keeping with observed difficulties shifting attention thought to use both dorsal and ventral systems (Rizzo and Vecera, 2002, Ricci et al., 2010, Ortibus et al., 2011a, Matsuba et al., 2006). Impaired selective attention, thought to use both dorsal and ventral systems (Ricci et al., 2006,

Saidkasimova et al., 2007) is seen in prematurely born children (Pasman et al., 1998), but the deficit may drop with age (Mulder et al., 2009). In contrast, sustained attention has been less clearly associated with premature birth in other studies (Mulder et al., 2009), although it is possible that a minority of prematurely born children having this deficit has masked the picture in other studies (Mulder et al., 2009).

5.3 Visual perceptual tests

5.3.1 Global motion

Impaired global motion perception is considered to be indicative of dorsal stream dysfunction (Milner and Goodale, 2006). In this present study global motion was used to assess perception of movement and visually guided movement. The average threshold for the prematurely born group was 23.8%, significantly poorer than controls at 18%. Cluster A children performed significantly worse than control children (two children in cluster A were unable to complete the task) but cluster B children performed no differently to controls. MacKay et al. (2005) measured the impact of premature birth on the development of first and second order local motion processing as well as global motion processing in a group of VLBW children. Assessment was performed using global motion stimuli. First order motion processing involves detection of luminance changes over a small area and being processed in the primary visual cortex and second order processing involves detection of changes other than luminance (such as contrast, depth or texture) and involving higher cortical processing. Global motion processing involves perceptual grouping of several local motion signals and involves the MT area. MacKay et al. (2005) reported three interesting findings: 1) there was a general deficit in all types of motion processing in the premature children not related to amblyopia, stereopsis or attention problems; 2) Despite this there was some segregation within the premature group of deficits in the 3 different types of motion processing supporting the idea that different neural mechanisms are involved; 3) Second order motion processing performance improved between the ages of 5 and 9 in the preterm children unlike the controls who were stable suggesting a delay rather than a permanent deficit. In contrast the global motion deficits were not only larger in magnitude in the preterm children but failed to show age related

improvement. These results are in accordance with the present study where prematurely born children had poorer scores than controls on global motion (p=0.001), with cluster A children performing significantly worse than controls. The two children unable to complete the test (N=2) belonged to cluster A. These data suggest that assessment of dorsal stream function may provide an objective marker for neurodevelopment in young children (MacKay et al., 2005).

5.3.2 Visual Closure (DTPV)

In this present study the DTPV subtest closure was used to assess the ability of a child to visualise a complete whole when given a partial picture. The prematurely born children (N=46) had a median standard score of 10 on the subtest closure (range 3-16) compared with a median score of 11, (range 2-16) for control children. These scores were not statistically significant (p=0.052), although on the border of being significant. Three-way comparisons of cluster A, B and controls did not identify any significant group differences.

Fazzi et al. (2004) investigated vision-perception in children with leucomalacia (N=20); the studied cohort were slightly younger than the present study with a mean age of 6.9 years (range 5 - 8 years) compared to 7.9 years (range 5.5 - 12 years) in the present study; mean gestational age 29.6 (range 25 - 33 weeks) versus 30.4 (24.0 – 34.6) in the present study; a mean birth weight of 1.5 kg (0.7 to 2.2 kg) versus 1.5 kg (0.6-2.4 kg) in the present study. Criteria for inclusion into Fazzi's study included: children presenting with spastic diplegia, PVL documented on MRI scan, normal or mildly impaired visual acuity with mild/moderate upper limb functional impairment. The profiles of the study groups studied in Fazzi's and the present study were similar for age, GA and birth weight. Differences in the profiles of the two cohorts were the study by Fazzi included infants with spastic diplegia, confirmed PVL and mild/moderate upper limb functional impairment. This indicates the subtle differences of timing, extent and location of insults to the developing foetus. Thirteen (65%) of the cohort studied by Fazzi's group scored poorly on the sub-test closure with a mean z score of -1.1 (SD 1.1), whereas in the present study 19 (41%) scored poorly with a mean z score of -0.23 (SD 0.8). The differences between the two studies could be attributed to the fact that Fazzi's group all had their diagnosis

confirmed by imaging, whereas the present study did not, therefore a confirmed imaging report was not available to confirm the exact location of any insult.

In Fazzi's cohort the location of insult was known, they had a slightly lower gestational age with the mean birth weight being similar in both studies (Fazzi et al., 2004).

5.3.3 Facial recognition

Deficits for global shape and face perception have been linked to VSD (Atkinson and Braddick, 2007). In this present study the T-score achieved for the facial recognition task in the preterm cohort was 44.8, lower than that of the controls at 50.0 ($p=0.03$). Cluster A children performed significantly worse than control children but cluster B children performed no differently to controls suggesting this test may be useful in identifying children with VSD. Published normative data are not available (Holiston 1999, Brekenridge, 2011, Atkinson, 2012).

5.3.4 Global form

Impaired global form is considered to be indicative of VSD (Milner and Goodale, 2006). In the present study the average threshold reached on the global form test for the prematurely born group was 16.8, poorer than that of the controls at 13.2. Cluster A children performed significantly worse than control children (two children in cluster A were unable to complete the task). Cluster B children performed no differently to controls. Braddick et al. (2000) have published work on visual perception in prematurely born children. Although they used different criteria (gestational age < 32 weeks), like the present study they found global form deficits.

These data suggest that VSD is particularly vulnerable during development, therefore early assessment of ventral stream function may provide an objective marker for neurodevelopment in young prematurely born and VLBW infants.

5.4 Ocular consequences of prematurity

5.4.1 Visual field deficits

Visual field analysis using the I4e Goldmann perimeter was feasible for over half of the children. Visual field abnormalities by confrontation were noted in four out of 33 of the prematurely born children in this present study, two each in cluster A and B. During structured clinical history taking, children would talk about missing the kerb and bumping into low objects such as plant pots, suggesting that a field loss, perhaps by neglect or inattention rather than by a visual field deficit. A simple, taught strategy of 'look down, check and go' can be useful while crossing the road and identifying where the kerb is, and is more helpful for children than the commonly-used phrase 'watch where you are going'. The data set for the Goldmann test was incomplete in the present study as many of the children lacked concentration or had poor fixation and were unable to complete the task. White matter damage of immaturity may affect visual fields, with the lower visual field more often affected than the upper (Jacobson et al., 2006).

5.4.2 Stereovision

Strabismus, reduced acuity and other ophthalmic problems associated with premature birth can reduce stereoacuity: a total absence of stereopsis was found in 12 % of prematurely born infants and abnormal stereopsis was present in 31% (Hard et al., 2000). This compares to a total absence of stereopsis in 9% of the present study, all of whom belonged to cluster A, and abnormal stereoposis in 11% of the total prematurely born cohort. Hard et al. used the Test for Stereoscopic Vision (TNO) to measure stereoacuity with objective decision limits for abnormality of ≥ 60 second of arc compared to the present study which used the Frisby test with a decision limit set at ≥ 70 second of arc. The study cohort of Hard et al. were all born before 29 weeks with a median age of 7.2 years (range 5.2-9.3 years). A direct comparison cannot be made with the present study as the study cohort tested were very premature and had a smaller age range. This, along with the fact two different tests were used, could explain their larger proportion of abnormal or absent stereopsis.

5.4.3 Ocular alignment

The present study reported 11.4% (N = 4/35) infants born prematurely as having strabismus, three with esophoria and one with convergence. This rate is lower than previously reported in other studies: O'Connor et al. (2002) reported 19.3% of low birth weight infants had strabismus compared to 3% of term born infants (O'Connor et al., 2002). Direct comparison is difficult between the two studies, although one explanation may be that in O'Connor's study the children were identified by birth weight, compared to gestational age in the present study; also the difference in sample size may have had an effect as O'Connor had a larger cohort (N = 293). However both studies highlight the increased incidence of strabismus in prematurely born children and babies who are born with low birth weight. These children may need to be screened and followed-up until the end of primary education. The numbers reported in the present study are low, with two being from each cluster A and B.

5.4.4 Eye movement problems

In the present study eye movement problems were recorded in 27% (N=3/11), of preterm infants, two of whom were in cluster A and one of whom was in cluster B, indicating perhaps that eye movement problems (and not CVI) are responsible for the visual difficulties experienced by some prematurely born infants. This may be a useful risk factor or early indicator of later perceptual and behavioural impairment.

A prospective study measuring smooth pursuit eye movements at 2 and 4 months in a cohort of very premature infants was undertaken by Strand-Brodd et al. (2011) in Norway during 2004-2007. Eighty-one prematurely born infants were studied and 32 healthy term infants comprised the control group. Mean gestational age for the study group was 28^{+5} weeks. At two and four months corrected age, prematurely born infants showed lower gain ($p<0.001$) and proportion of smooth eye movements ($p<0.0001$) compared to the control group. The authors concluded that oculo-motor development measured by smooth pursuit eye movements is delayed in very preterm infants at two and four months corrected age.

5.4.5 Contrast sensitivity

O'Connor et al. (2004) undertook a study to compare contrast sensitivity in prematurely born and term born children; the former had significantly lower contrast sensitivity. Although there was a statistically significant difference between the two groups ($p < 0.001$ for all measures), this difference was subtle (one to two letters) (O'Connor et al., 2004). Thirteen percent (5/38) of the prematurely born children in the present study had abnormal contrast sensitivity scores: of these, four belonged to cluster A (4/11) and one (1/27) to cluster B (Fisher exact test, $p = 0.019$). The objective decision limit for abnormality was < 1.75% in both studies utilising the Peli-Robson sensitivity chart which uses letters of low spatial frequency, therefore results are likely to be less affected by mild acuity losses such as those demonstrated in the low birth weight cohort of O'Connor et al., suggesting that the measurement tool may not be sensitive enough to detect small changes in contrast sensitivity. Although small and independent of VA, reduced contrast sensitivity may signify subtle underlying adverse effects of preterm birth and neurological development.

5.4.6 Colour Vision

Ishihara scores (a test with crowded elements) were higher for children in cluster A and overall scores were equivocal in 20/33 children tested, indicating that Ishihara may be able to identify visual crowding in children born prematurely, but not sufficiently well to be a test for this problem.

5.5 Intelligence testing (Kaufmann Brief Intelligence Test)

Forty-four children completed the IQ test (not carried out on two children one from each cluster, as test equipment was unavailable during their visit). Standardised scores ranged from 59 to 118, with a median value of 85. Median IQs for cluster A (84.5; range 59-114) and cluster B (86.5; range 64-118) were not statistically different ($p = 0.75$). The results of the present study are in accordance with other studies. Research has consistently demonstrated a greater risk for learning related problems in preterm and LBW children as they progress through school (Escobar et al., 1991, Cooke et al.,2004, Marlow et al,. 2007, Johnson et al., 2009).

A meta-analysis by of studies examining school-age children born preterm found that prematurely born children exhibited significantly lower IQ scores than full-term controls (Bhutta et al., 2002). Grunau et al. (2002) reported that 9-year-old ELBW children's mean Full Scale, Verbal, and Performance IQ scores were 15 to 17 points lower than those of full-term controls. Among the children with ELBW, 19% had either a Verbal or Performance IQ score in the below average range (<85) compared with 3% of the control group. Hack (2006) looked at IQ scores at 20 years of age and found that VLBW young adults demonstrated a significantly lower mean IQ score than full-term controls (87 v92; $p < 0.001$). This considerable discrepancy between the overall rates of below average IQ scores could be because the Hack et al. cohort included children with neurosensory impairments such as blindness, hearing loss, and cerebral palsy, while the Grunau et al. study excluded such children. Furthermore, differences in the socioeconomic status of the two study cohorts may have contributed to the substantial discrepancy in the rates of below average IQ. In particular, participants in the Grunau et al. study were predominantly middle class, whereas Hack included more lower-income participants (Hack, 2006). The present study demonstrated similar results.

5.6 Limitations of study

This study concerns a very important and overlooked type of complex visual difficulty seen in children with brain damage. One of the limitations of the study is that a full systematic validation of the CVI questionnaire has not yet been done, but a partial validation has been carried out (Macintyre-Beon et al., 2012).

The CVI questionnaire has potential to be a unique tool to helping identify significant complex visual problems in children with a history of brain damage. With further development for example Rasch analysis (Rasch, 1960), which is recognised as perhaps one of the best models to evaluate and reframe subjective rating scales, eliminating redundant items and providing useful combinations, eventually leading to a refined measure of behaviour may be worthwhile considering to perform on the CVI questionnaire in the future, as the next stage of developing the questionnaire as a Gold Standard in the screening of children for CVI.

The assumption that the control group had no neurodisability was based on a lack of learning support in school, which is not determined by level of learning ability or child-specific factors alone but multiple factors including funding and availability.

The apportionment of “worst scores” to children who could not perform the attentional and visual perceptual tests was assumed to produce less bias than their removal. As each child attempted the test, it was decided that they should be included. Removal would have biased the results towards better group performance, so as the children could not complete the test they were apportioned a “worst score”.

Not all visual function tests were completed on all 46 study group children. The reasons for this for the 11 children concerned were as follows: 6 were unable to complete testing due to poor concentration; a set of triplets participated in the attention and visual perceptual testing but had moved to Ireland and were unable to attend for ophthalmological testing with the ophthalmologist; two children were not contactable.

The study group did not receive any form of imaging therefore the researchers did not know which children had PVL. However, this was discussed during the early developmental stages and for the purpose of this study was deemed not to be ethical as it would not change clinical management for the child or their ongoing care.

Other potential sources of bias in the present study were that those who declined to take part in the study were from areas of higher social deprivation than those who agreed to take part. As less deprivation is associated with lower morbidity (Carstairs and Morris, 1991), the incidence of visual disability might have been even higher if all children invited to participate had attended. The relationship between social deprivation and CVI is not known; however, it is reasonable to hypothesise that greater deprivation is associated with higher prevalence of CVI, therefore 33% prevalence in the prematurely born cohort may be an underestimate.

5.7 Conclusion

The study hypothesis set out in Chapter 2 was that "Children born prematurely are at increased risk of CVI" and the aim of the study was to "Identify whether children born prematurely are at increased risk of CVI".

This study is the first systematic investigation of the CVI questionnaire in a well-defined clinical population focussing on a cohort of children prematurely born who were known to be at increased risk of CVI. To date no scientific study had been undertaken to assess the incidence of CVI in this population. One third of prematurely born children studied revealed evidence of CVI, estimating the incidence of CVI in prematurely born children as between 21- 47% (95% CI).

CVI is not a deficit of all prematurely born children in general, but rather of only a minority as demonstrated by the cluster analysis, which showed that structured history taking is effective in discriminating affected from unaffected children as a freestanding observation. The investigations carried out were chosen to match the appropriate subsection of the CVI questionnaire. Whilst they corroborate the history taking results in groups of children, showing that those with histories of difficulty do manifest abnormalities of both primary visual functions and visual perception, none of these investigations was sufficient to either identify all affected cases or to characterise the visual problem.

Currently available perceptual tests appear to be insufficiently sensitive to find and identify the specific pattern of problems noted in this group. However, the CVI questionnaire (with further work on validation), has the potential to be a unique clinical tool in helping identify children at risk.

Impaired global motion perception, indicative of DSD (Braddick et al., 2000) was seen in cluster A children, suggesting that the deficit may be permanent rather than a delay of maturation (Birtles et al., 2007).

Impaired global form perception and face recognition indicative of VSD (Goodale and Milner, 1992), was also seen in cluster A children. The inability to recognise faces, as well as the language conveyed by facial expression is particularly disabling for affected children. However, only three children in cluster A demonstrated recognition difficulties using the CVI questionnaire suggesting

further work needs to be carried out to identify appropriate questions to identify recognition difficulties.

This study leads to the conclusion that there is an urgent need to improve the design of investigations that identify visual behaviours elicited by history taking.

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Appendices

Appendix 1

Professionals CVI Inventory Version 2 August 2008

About your child

Child's initials:_____

Child's D.O.B.:_____

Child's gender:_____

Is your child right or left handed?_____

How many weeks into your pregnancy were you when you gave birth?

_____

Were there any problems at the time of birth? If so, please describe:

_____

_____

Has your child had any conditions affecting the eyes or brain? If so, please describe:

_____

_____

Do you have any concerns about your child's vision? If so what are they?

_____

_____

Instructions to parents

We want to find out what children at different ages can and cannot see. We want to know about how your child behaves **now** but not when younger.

These questions are designed for a range of ages, so some questions may seem odd. Your child may have difficulty with some behaviours listed below but not others – this is normal.

Also you may notice that some of the behaviours described occur occasionally when your child is tired, this is common.

For each of the items listed, please could you tick the box which best fits with your child's **present** behaviour.

never/ rarely/ sometimes/ often/ always/ not applicable (NA)

The Cerebral Visual Impairment Inventory. To each question, patients tick "never", "rarely", "sometimes", "often" or "always".

a) Questions seeking evidence of visual field impairment or impaired visual attention on one or other side. Does your
1. trip over toys and obstacles on the floor?
2. have difficulty walking down stairs?
3. trip at the edges of pavements going up?
4. trip at the edges of pavements going down?
5. appear to 'get stuck' at the top of a slide/ hill?
6. look down when crossing floor boundaries e.g. where lino meets carpet?
7. leave food on the near or far side of their plate? If so, on which side (near/far)
8. leave food on the right or left side of their plate? If so, on which side (left/right)
9. have difficulty finding the beginning of a line when reading?
10. have difficulty finding the next word when reading?
11. walk out in front of traffic? If so, on which side (left/right)
12. bump into doorframes or partly open doors? If so, on which side (left/right)
13. miss pictures or words on one side of page? If so, on which side (left/right)
b) Questions seeking evidence of impaired perception of movement. Does your child….
14. have difficulty seeing scenery from a moving vehicle?
15. have difficulty seeing things which are moving quickly, such as small animals?
16. avoid watching fast moving TV?
17. choose to watch slow moving TV?
18. have difficulty catching a ball?
c) Questions seeking evidence of difficulty of handling complexity of a visual scene. Does your child….
19. have difficulty seeing something which is pointed out in the distance?
20. have difficulty finding a close friend or relative who is standing in a group?
21. have difficulty finding an item in a supermarket , e.g. finding the breakfast cereal they want?
22. get lost in places where there is a lot to see, e.g. a crowded shop?
23. get lost in places which are well known to them?
24. have difficulty locating an item of clothing in a pile of clothes?
25. have difficulty selecting a chosen toy in a toy box?
26. want to sit closer to the television than about 30cm?
27. find copying words or drawings time-consuming and difficult?
d) Questions seeking evidence of impairment of visually guided movement of the body and further evidence of visual
28. When walking, does your child hold onto your clothes, tugging down?
29. Does your child find uneven ground difficult to walk over?
30. Does your child bump into low furniture such as a coffee table?
31. Is low furniture bumped in to if it is moved?
32. Does your child get angry if furniture is moved?
33. Does your child explore floor boundaries (e.g. lino/carpet) with their foot before crossing the boundary?
34. Does your child find inside floor boundaries difficult to cross?
If so… boundaries that are new to them?
…boundaries that are well known to them?
35. Does your child reach incorrectly for objects, that is, do they reach beyond or around the object?
36. When picking up an object, does your child grasp incorrectly, that is do they miss or knock the object over?
e) Questions seeking evidence of impaired visual attention
37. Does your child find it difficult to keep to a task for more than 5 minutes?
38. After being distracted does your child find it difficult to get back to what they were doing?
39. Does your child bump into things when walking and having a conversation?
40. Does your child miss objects which are obvious to you because they are different from their background and seem to
f) Questions seeking evidence of difficulties associated with crowded environments
41. Do rooms with a lot of clutter cause difficult behaviour?
42. Do quiet places / open countryside cause difficult behaviour?
43. Is behaviour in a busy supermarket or shopping centre difficult?
44. Does your child react angrily when other restless children cause distraction?
g) Questions evaluating the ability to recognize what is being looked at and to navigate. Does your child…
45. have difficulty recognising close relatives in real life?
46. have difficulty recognising close relatives from photographs?
47. mistakenly identify strangers as people known to them?
48. have difficulty understanding the meaning of facial expressions?
49. have difficulty naming common colours?
50. have difficulty naming basic shapes such as squares, triangles and circles?
51. have difficulty recognising familiar objects such as the family car?

NHS Greater Glasgow and Clyde

Appendix 2

PERCEPTUAL VISUAL PROBLEMS IN CHILDREN BORN PREMATURELY: ARE THEY DUE TO DORSAL STREAM DYSFUNCTION?

Version 3 - 25th August 2008
Research Participants Information Sheet

{Information sheet for Parents of Children under 8 years}

Invitation

Your child is being invited to take part in a research study. Before you decide it is important for you to understand why the research is being done and what it will involve. Please take time to read the following information carefully and discuss it with friends, relatives and your child's GP if you wish. Ask us if there is anything that is not clear or if you would like more information. Take time to decide whether or not you wish your child to take part; you have as much time as you wish to decide.

What is the purpose of this study?

As you know, your child's vision has been tested and you have given a detailed history taking about your child's vision as part of his/her management. As a result we would like to do some more tests on your child's vision. We hope that this wil allow us to diagnose visual problems in other children more easily, as well as allowing us to suggest better ways of helpin your child's vision.

Does my child have to take part?

No. It is up to you whether or not your child should take part. If you decide to join the study you will be given this information sheet to keep and be asked to sign a consent form. If you do decide for your child to take part you are still fre to withdraw at any time and without giving a reason. A decision to withdraw at any time, or a decision not to take part, wi not affect the standard of any care you or your child receive.

What will happen to my child if they take part and what do they have to do?

We would like your child to complete some 6 vision and IQ tests which are in addition to their usual clinical assessment. We ask that they come to the hospital twice, each time for about 45 minutes to one hour.

What are the possible disadvantages and risks of taking part?

These tests will take around an hour and a half to two hours to complete.

What are the possible benefits of taking part in this study?

The results of the vision tests will be used to show you how you can help your child.

What if something goes wrong?

We are not aware of any risks from doing these tests. The only thing that could happen is that a technical problem could make the test last longer.

If your child is harmed by taking part in the research project, there are no special compensation arrangements. If they are harmed due to someone's negligence, then you may have grounds for a legal action but you may have to pay for it.

If your child is harmed by taking part in the research project, there are no special compensation arrangements. If they are harmed due to someone's negligence, then you may have grounds for a legal action but you may have to pay for it. Regardless of this, if you wish to complain, or have concerns about any aspect of the way you or your child have been approached or treated during the course of this study, the normal National Health Service complaints mechanism is available to you.

The Yorkhill Division NHS Greater Glasgow aims to provide a warm and welcoming atmosphere. We are always happy to improve our service, therefore we would like to hear from you if you have suggestions for improvement, or you have a query or criticism about any aspect of our service. Please do not hesitate to speak to a member of staff about any problems which you identify. She/he will help whenever possible and bring your concerns to the Head of Department. If you have any reason to complain, please contact Mrs. Kate Colquhoun, Complaints Officer, Yorkhill Hospital at 0141 201 0000, who has the role of dealing with any complaints on a formal basis.

Will my child's taking part be kept confidential?

All the information that we collect about your child will be kept strictly confidential. For the purpose of this research, any information about your child's data which leaves the hospital or university will have their name and address removed so that they cannot be recognised from it. The information held in the hospital and university may be looked at by regulatory authorities to check that the study is being carried out correctly.

If we find during this study that your child's vision has any abnormalities we will tell your family Doctor.

If you agree for your child to take part in this study, we are obliged, with your approval, to inform your child's G.P. and we will give you a letter to give to their G.P.

What will happen to the results of this study?

The results of the study will be discussed at medical meetings and may be published in a medical journal. Your child will not be identified at any time.

Who is organising this research?

This has been organised by the Paediatric Epidemiology and Community Health (PEACH) Unit, the Neonatal Unit, Queen Mothers Hospital, Glasgow and the Department of Vision Sciences at Glasgow Caledonian University. We have been given a grant to do this study and the people who hold the grant are: Professor David Stone, The PEACH Unit, University of Glasgow.

The Chief Scientists Office Edinburgh awarded the grant.

Who has reviewed the study?

The study has been reviewed by the Yorkhill Research Ethics Committee.

If you want to contact us about the study the number is: CZG_2_370

For any further information please contact: Catriona Macintyre-Beon, Research Fellow, Glasgow University 0141 201 0178 (24 Hour Answer phone).

If you have any reason to complain, please contact Mrs. Kate Colquhoun, Complaints Officer, Yorkhill Hospital at 0141 201 0000, who has the role of dealing with any complaints on a formal basis.

Thank you for reading this information sheet

If you agree to take part you will be given this information sheet and a signed consent form to keep

Dorsal Stream Dysfunction in Children Born Pre-term: Identification, Characterisation and Management

Version 3 – 25th August 2008

CONSENT FORM FOR PARENTS/GUARDIANS OF CHILD VOLUNTEERS

Please initial boxes

1. I confirm that I have read and understood the information sheet dated

Version 3 – 25th August 2008

for the above study and have had the opportunity to ask questions. ☐

2. I understand that my child's participation is voluntary and that I am free to withdraw them at any time without giving any reason, without our medical care or legal rights being affected. ☐

3. I agree to my child take part in the above study. ☐

_____	_____	_____
Name of volunteer	Date	Signature

_____	_____
Date of birth	Home address

_____	_____
Name of GP	GP address

_____	_____	_____
Name of parent/guardian	Date	Signature

_____	_____	_____
Name of person taking consent	Date	Signature

_____	_____	_____
Witness	Date	Signature

1 copy for volunteer, 1 copy for researcher

Appendix 3

PERCEPTUAL VISUAL PROBLEMS IN CHILDREN BORN PREMATURELY:

ARE THEY DUE TO DORSAL STREAM DYSFUNCTION?

Version 3 – 25th August 2008

{Information sheet for Child Volunteers ages 8 - 12 Years}

We would like to ask you to join a research study and before you join we would like to explain why and how the research is being done. Please take time to read this information and if there is anything you do not understand please ask us.

What is the purpose of this study?

We know that you see the world in a special way. We want to understand this. We can tell your parents/carers and teachers about your special vision. They can then make sure that you can get the most out of what you see.

Why have I been chosen?

Because you have a kind of special vision which we want to understand better and to find out what questions to ask parents to decide best what type of vision their children have.

Do I have to take part?

No. It is up to you whether you take part or not. If you decide to join the study you can leave at any time without telling us why.

What will happen to me if I take part?

The tests we want to do will not hurt you. We would like you to complete some tests of how you see, which are in addition to your usual tests. We ask that you come to the hospital twice, each time for about 45 - 60 mins.

What are the possible disadvantages of taking part?

These are mainly your time. However, the children's tests are easy to perform therefore it is anticipated that no problems will arise as a result of taking part.

These tests will take around an hour and a half to two hours to complete.

What are the possible benefits of taking part in this study?

The results of the tests will be used to show how your parents/carers/teachers can help you.

What if something goes wrong?

We do not know of any risks from doing the tests. The only thing that could happen is that a technical problem could make the test last longer.

If you are not happy about the way this study is carried out you can complain to a Complaints Officer at Yorkhill. She is Mrs Kate Colquhoun, Yorkhill Division, Yorkhill, Glasgow G3 8SJ. You can also phone Glasgow Health Council 0141 201 4444.

Will my taking part be kept confidential ?

All the information that we collect about you will be kept strictly private, contained in a locked filing cabinet or in password protected files at Yorkhill Hospital. Your name and address will not appear on any of the papers we use for the study.

If we find during this study that your vision has a problem we will tell your family Doctor.

If you agree to join this study, with your permission we will tell your family Doctor that you have joined.

What will happen to the results of this study ?

The results of the study will be discussed at medical meetings and may be published in a medical journal. You will not be identified at any time.

Who is organising this research?

This has been organised by the Paediatric Epidemiology And Community Health (PEACH) Unit, the Neonatal Unit, the Queen Mothers Hospital and Yorkhhill Childrens Hospital, Glasgow. We have been given a grant to do this study and the people who hold the grant are: Professor David Stone The PEACH Unit, University of Glasgow. In addition, Catriona Macintyre-Beon is doing a Ph.D. on this topic and this study will form part of it.

The Chief Scientists Office Edinburgh has awarded the grant.

Who has reviewed the study?

The study has been reviewed by the West Glasgow Research Ethics Committee.

If you want to contact us about the study the number is: CZG_2_370

For further information please contact Catriona Macintyre-Beon, Research Fellow, Glasgow University, 0141 201 0818 (24 Hour Answerphone)

Thank you for reading this information sheet

If you agree to take part you will be given this information sheet and a signed consent form to keep

Dorsal Stream Dysfunction in children born pre-term: Identification, Characterisation and Management

Version 3 – 25th August 2008

ASSENT FORM FOR CHILD VOLUNTEERS

Please initial boxes

1.	I confirm that I have read and understood the information sheet dated 25th August 2008 for the above study and have had the opportunity to ask questions.	☐
2.	I understand that my participation is voluntary and that I am free to withdraw at any time without giving any reason, without my medical care or legal rights being affected.	☐
3.	I agree to take part in the above study.	☐

_____	_____	_____
Name of volunteer	Date	Signature
_____	_____	
Date of birth	Home address	
_____	_____	
Name of GP	GP address	
_____	_____	_____
Name of person taking consent	Date	Signature
_____	_____	_____
Witness	Date	Signature

1 copy for volunteer, 1 copy for researcher

Appendix 4

PERCEPTUAL VISUAL PROBLEMS IN CHILDREN BORN PREMATURELY: ARE THEY DUE TO DORSAL STREAM DYSFUNCTION?

Date:

Parents Name and Address:

PERCEPTUAL VISUAL PROBLEMS IN CHILDREN BORN PREMATURELY :

ARE THEY DUE TO DORSAL STREAM DYSFUNTION

Subject Name: Date of Birth:

Dear

The Ophthalmology Department at Yorkhill Hospital in conjunction with the neonatal unit at The Queen Mothers Hospital are investigating children who have been born prematurely to asses their vision as your child is currently being followed up at the Developmental Clinic we would like to invite you to take part in the above study. If you would be interested in participating or would like further information please contact me on: 0141 201 0178 or email me at cmacintyre-beon@nhs.net.

I have attached an information sheet which will give you further information on what participation to this study would include.

Yours sincerely

Catriona Macintyre-Beon
Research Fellow
PEACH Unit
Department of Child Health
University of Glasgow
Yorkhill Hospital
Glasgow G3 88J
Tel: 0141 201 0178
Email: cmacintyre-beon@nhs.net

PERCEPTUAL VISUAL PROBLEMS IN CHILDREN BORN PREMATURELY: ARE THEY DUE TO DORSAL STREAM DYSFUNCTION?

Date:

Parents Name and Address:

PERCEPTUAL VISUAL PROBLEMS IN CHILDREN BORN PREMATURELY :
ARE THEY DUE TO DORSAL STREAM DYSFUNTION

Subject Name: Date of Birth:
Address:

We are investigating children with visual problems associated with the dorsal stream which serves visual attention and visual guidance of movement. This entails carrying out some standard cognitive vision tests as well as some computer based vision tests. I enclose a participant information sheet

For your information, the above subject, who is one of your patients, has kindly agreed to take part.

Yours sincerely

Catriona Macintyre-Beon
Research Fellow
PEACH Unit
Department of Child Health
University of Glasgow
Yorkhill Hospital
Glasgow G3 88J

Appendix 6

Dear John Simmons,
Head of Education, East Dunbartonshire Council

Re: Proposed vision study in local primary schools

As previously discussed via email, please find below a description of our proposed vision study. I wasn't sure how much detail you require – please let me know if you need further information on any aspect of the proposed study.

Kind Regards,

Dr. Julie Calvert

Background

The Royal Hospital for Sick Children and Glasgow Caledonian University have been given joint funding from Medical Research Scotland for a two year study investigating visual dysfunction in children (Title: Dorsal Stream Dysfunction in Children: Identification, Characterisation and Management).

The visual brain contains two pathways, the ventral and dorsal streams, each serving different visual functions. The dorsal stream processes information on spatial properties of objects and their motion, while the ventral stream processes information about surface properties of objects such as shape and colour.

A questionnaire (questionnaire enclosed) has been developed from experience of taking histories from the parents of many hundred children with visual problems due to damage to the brain areas responsible for complex visual functions. Many years of clinical experience at Yorkhill Hospital, Glasgow has revealed that many children with early brain damage have a symptom complex which may be explained by damage to the dorsal stream. Children who are at risk include those who have been born very prematurely, who have hydrocephalus, cerebral palsy, who have recovered from infection, who have been born with structural or functional disorders of the tissues of the brain as well as those without any known cause. This questionnaire produces a full description of the specific visual problems of this group of children.

Overall aim of study

The overall aim of our project is to validate this questionnaire. We will do this by comparing the results of the questionnaire with standard tests of visual function. In addition, our aim is to identify a visual test which can identify this group of children.

Our aim is to provide vision clinics with an objective and rapid tool they can use to identify an, as yet, unlabelled symptom complex in children presenting with visual problems. We know that vision is vital in child development and so identifying children with the dysfunction as early as possible can help to provide them with habilitative strategies which will aid their intellectual, educational and social development.

Aim of accessing healthy children from local schools

We wish to test 120 primary school age healthy children and their parents, in order to provide control information on what is normal visual behaviour at different ages.

Investigators

The investigators are Dr. Julie Calvert (Research Fellow, Glasgow Caledonain University/Yorkhill Hospital,) and Professor Gordon Dutton (Paediatric Ophthalmologist, Yorkhill Hospital, Professor, Glasgow Caledonian University). The vision tests we will carry out will be performed by Dr. Calvert and Catriona Macintyre-Beon (Research Midwife, Yorkhill Hospital). Both researchers have Disclosure Scotland and many years experience working with children. We have ethical approval from the NHS Research Ethics Committee and from Glasgow Caledonian University's Ethics board to carry out this project.

What we plan to do in the schools

1. Seek formal approval from Head teachers of local primary schools. Three schools (Castlehill, Clober and Bearsden) have already shown interest in taking part, given your approval.

2. Send out information sheets and consent forms to a number of parents within each participating school (information sheet and consent form enclosed). These will be sent home with the children.

3. For the parents who consent –

A questionnaire will be sent home with the child for the parent to complete and return (questionnaire enclosed).

Each child will be tested on a number of visual tests. Tests children will carry out:

<u>Tests of basic visual function</u>

What we will assess: visual acuity, visual field.

These tests are brief and non-invasive. Visual acuity is measured by the standard letter chart test you find in the optician's. Visual field testing assesses whether the child can see objects in each of the four quadrants of their visual field. We will do this by presenting an object in front of the child (either to their upper right, upper left, lower right or lower left corners of sight) and asking if they can see it.

Computer-based tests

What we will assess: motion and form sensitivity. All tests are presented as games and children have previously reported that they enjoy these tasks.

Paper and pencil tests

What we will assess: attention, face recognition, visual perception

We estimate that the testing will take around 1 hour per child. We plan to discuss with each head teacher how much time they would like each child to sit for and how many children they would like to participate.

GLASGOW CALEDONIAN UNIVERSITY

Appendix 7

Letter to schools who have previously given informal consent

Westerton Primary
Crarae Avenue, Bearsden G61 1HY
office@westerton.e-dunbarton.sch.uk

Dear Mr Oakes,
Re: Vision study
Establishing age-related normal values for children performing some simple visual tasks.

As we have recently discussed, we are now formally writing to ask if you would consider some of your children participating in a vision study being carried out by the Royal Hospital for Sick Children together with the Department of Vision Sciences, Glasgow Caledonian University. We would like to test children from age 4 to 12 years. The team consists of myself, Dr. Julie Calvert, with ten years experience in testing vision, Prof. Gordon Dutton, a Paediatric Ophthalmologist and Catriona Macintyre-Beon, a research midwife with 25 years NHS experience, from Yorkhill Hospital. Last year we carried out a successful vision study with St. Andrew's Primary School, Bearsden.

The overall aim of the project is to investigate visual problems in children who have been born prematurely. Some of the problems they have are as follows:

Difficulty differentiating between floor boundaries and steps, problems identifying their mother when she is standing in a group of people and problems with reading. We have devised a way of testing these children's vision. However, in order to grade their scores, we need to know how vision develops in healthy children of different ages.

We would like to test healthy children on a number of vision tests (e.g. face recognition abilities, sensitivity to motion). These tests are non-invasive and they are presented to the children as games. Catriona's children have already done some of the tests and say they had fun! In addition, we would like to send out a questionnaire to parents of the children we test to assess their views on their children's vision (in the future we hope this questionnaire will be used in clinics across the world to identify children with the problems described above).

I would like to stress that this study will not directly benefit the children and is not a sight test or health assessment. Our aim is to collect information about the normal, healthy range of visual responses. Then, we can compare the responses of children with potential visual problems attending Yorkhill Hospital, with our range of normal responses. This will aid diagnosis and treatment. It is vital that we are able to identify children who have this problem so we can provide support for them in their daily lives. Their condition means that they are often wrongly judged to have poor intellectual performance or behaviour. Our research also aims to identify strategies that can be put into practice to provide children with coping strategies that will support their intellectual, educational and social development.

We very much hope that you can assist us in our research by considering our request and discussing it with the class teachers. I am very happy to come to the school at your convenience to further discuss the proposed project with you and/or any class teachers. Could you please advise me on the suitability of this project for your children and whether we can proceed.

Yours sincerely,

Dr. Julie Calvert
Vision Researcher, Study Co-ordinator
Telephone: 0141 331 3108 (direct)
0141 331 3379 (departmental Secretary)
Email: j.calvert@gcal.ac.uk

Professor Gordon Dutton
Paediatric Ophthalmologist

Catriona Macintyre-Beon
Research Midwife

GLASGOW CALEDONIAN UNIVERSITY

Information and Consent for Volunteers participating in Research

Establishing age-related normal values for children performing some simple visual tasks.

Investigators:
Julie Calvert (Study Coordinator)
email: j.calvert@gcal.ac.uk
tel: 0141 331 3108

Professor Gordon Dutton
tel: 331-3379 (secretary)

INTRODUCTION

The Department of Vision Sciences at Glasgow Caledonian University is currently investigating the special visual difficulties experienced by some children with a condition called peri-ventricular white matter disease. However, we need in the first instance to gain more information about the vision of healthy children, in order to make a comparison with patients who may have peri-ventricular white matter disease. We hope that this information will help us to devise the best ways to identify patients with this condition in the future and to allow us to help them cope in their everyday lives.

These notes are intended to inform you and your child about what you would be expected to do, in order that you can make up your mind about whether you and your child would wish to take part in the study.

It is important that you know that any participation is voluntary and that, even if you do decide to go ahead, you can withdraw at any time.

SUBJECT GROUP

We hope to recruit 120 primary school age children and their parents to take part in this study.

WHAT IS INVOLVED?

You will be asked a number of questions about your child's vision e.g. 'Does your child have difficulty seeing from a moving car?'

Your child will be asked to undertake a number of simple vision tests (with their glasses or contact lenses if worn). These will include the standard letter chart found in the optometrist's, some brief paper and pencil tasks and a straightforward

task on a computer. An investigator will be present during the testing session to guide your child through the procedures.

BENEFITS

This is purely a research study and it is likely that there will not be any direct benefit to you/your child for taking part.

POSSIBLE ADVERSE EFFECTS

The parent questionnaire is brief and the children's tests are easy to perform and it is anticipated that no problems or adverse effects will arise as a result of taking part.

CONFIDENTIALITY

The identity of you and your child will not be revealed in any publications that arise from this work.

FURTHER INFORMATION

You may contact the investigators at any time if you have questions about the study.

CONSENT

We would like you to sign the following declaration if you and your child are willing to take part. Signing this consent form does not commit you/your child to completing the study but is a statement recognising that you have had the study explained to your satisfaction.

DECLARATION

I agree to take part in the study outlined above, and understand the information that has been provided.

Print name:

Signed:

Date:

Appendix 9

Letter to GP

Project title: Characterising the Syndrome Complex of Dorsal Stream Dysfunction

Royal Hospital for Sick children, Yorkhill Hospitals, Glasgow G3 8SJ Tel: 0141 201 0818

Date xxxx

Dear (GP's name)

Project title: Characterising the Syndrome Complex of Dorsal Stream Dysfunction

xxxxxxxxxxx, a patient of yours, has volunteered to take part in the above study, and has requested that we let you know.

I enclose an Information Sheet for the study as part of this letter.

You are very welcome to get in touch if there is anything you would like to ask about the study. If you telephone Catriona Macintyre-Beon our Research Fellow on 0141 201 0178 she will be able to answer any queries you may have.

Yours sincerely

Professor Gordon Dutton

Paediatric Ophthalmologist

Appendix 10

Score Sheet for Testing

Initials_____ **Today's date**_____

DOB_____ **Age** _____years **Gender**_____

VA **GAC** **Viewing distance: 3m**

Right eye_____

Left eye_____

Binocular_____

Comments:

Stereoacuity **Frisby Test** **Viewing distance: 40cm**

30secs/arc 	30secs/arc 
15secs/arc 	15secs/arc 

Stereoacuity_____secs/arc

Comments:

Global form **Viewing distance:40cm**

File number_____

Threshold_____%

Global motion

File number_____

Threshold_____%

Comments:

DTVP - Closure **Viewing distance: not specified**

1	2	3	4	5	6	7	8	9	10

11	12	13	14	15	16	17	18	19	20

Score_____ Number wrong _____ What questions?_____

Comments:

Attention

1. Selective attention Version_____

TEA-Ch: Sky search

Number circled:_____ Time:_____

Number circled:_____ Motor time:_____

Strategy (eg. systematic/impulsive/overcautious):_____

_____

2. Attentional control

TEA-Opposite worlds

Same A/1_____

Opposite A/2_____

Opposite A/3_____ Same world total time_____

Same A4_____ Opposite world total time_____

3. Sustained attention

TEA- Score! Version_____

Number counted

Game 1	Game 6
Game 2	Game 7
Game 3	Game 8
Game 4	Game 9
Game 5	Game 10

Number correct_____/10

4. Divided attention (visual & auditory) Version_____

TEA- Sky search DT

Number circled:_____ Time:_____

Strategy (eg. systematic/impulsive/overcautious):_____

_____

Number counted

Game 1	Game 6
Game 2	Game 7
Game 3	Game 8
Game 4	Game 9
Game 5	Game 10

Number correct:_____/_____

Face recognition **Viewing distance: not specified**

Idmatch.dis (practice trial first)

practice	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16
l	l	r	l	r	r	l	l	l	l	r	r	l	r	r	l	r

Score = _____/16____

START HERE

Idmatch.sim (practice trial first)

practice	4	3	1	6		2	5	7	8	9	10	11	12	13	14	15	16
l	r	l	l	l		r	r	l	r	l	l	r	l	r	r	l	r

Score = _____/4 or _____/16____

Idno.dis (practice trial first)

practice	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16
l	l	l	r	r	r	l	l	r	r	l	r	r	l	r	l	l

Score =_____/16____

Idno.sim

1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16
r	r	l	r	r	l	r	l	r	l	r	l	l	r	r	r

Score = _____/16____

Idmask.sim

1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16
r	r	l	l	l	l	l	l	r	l	r	l	r	r	l	r

Score = _____/16____

Total score =_____/80____ success = 13/16

Comments:

Kaufman BIT-2 (matrices)

Sample A 1-9 (age 4-7 years)

example	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**

Sample B 10-22 (age 8-90 years)

example	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**	**18**

19	**20**	**21**	**22**

Sample C 23-46

example	**23**	**24**	**25**	**26**	**27**	**28**	**29**	**30**	**31**

32	**33**	**34**	**35**	**36**	**37**	**38**	**39**	**40**

41	**42**	**43**	**44**	**45**	**46**

Appendix 11

Summary output from Cluster analysis, applying Ward linkage and squared Euclidean distance. Minitab 16.

	Number of observations	Average Within cluster sum of squares	Maximum distance from centroid	Maximum distance from centroid
Cluster1	31	180.516	2.28269	4.05798
Cluster2	15	427.867	5.26105	6.47113

Cluster Centroids

Variable	Cluster1	Cluster2	Grand centroid
q1	1.48387	3.40000	2.10870
q2	1.03226	2.66667	1.56522
q7	1.06452	1.93333	1.34783
q8	1.12903	1.86667	1.36957
q11	1.22581	2.33333	1.58696
q12	1.45161	2.80000	1.89130
q15	1.22581	2.53333	1.65217
q18	1.51613	2.53333	1.84783
q19	1.48387	3.33333	2.08696
q20	1.22581	3.13333	1.84783
q22	1.29032	3.26667	1.93478
q24	1.32258	3.86667	2.15217
q25	1.19355	3.26667	1.86957
q26	1.70968	3.13333	2.17391
q28	1.22581	2.60000	1.67391
q29	1.12903	2.86667	1.69565
q36	1.16129	2.60000	1.63043
q37	1.58065	3.53333	2.21739

Distances Between Cluster Centroids

	Cluster1	Cluster2
Cluster1	0.00000	6.92702
Cluster2	6.92702	0.00000