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Glossary of abbreviations

ASD	**Autism Spectrum Disorders**
BVA	**Binocular Visual Acuity**
CAC	**Cardiff Acuity Cards**
CHYLD	**Children with Hypoglycaemia and their Later Development**
ETDRS	**Early Treatment Diabetic Retinopathy Study**
FPL	**Forced Preferential Looking**
IP	**Intra Parietal Area**
IQR	**Interquartile range**
IT	**Infero Temporal Area**
JCC	**Jackson Cross Cylinder**
LGN	**Lateral Geniculate Nucleus**
logMAR	**Logarithmic of Minimum Angle of Resolution**
LS	**Lea Symbols**
MAR	**Minimum Angle of Resolution**
MCT	**Motion Coherence Threshold**
MRI	**Magnetic Resonance Imaging**
MT	**Middle Temporal Area**
NH	**Neonatal Hypoglycaemia**
OKN	**Optokinetic Nystagmus**
PL	**Preferential Looking**
RDK	**Random Dot Kinematogram**
TAC	**Teller Acuity Cards**
VA	**Visual Acuity**
VEP	**Visual Evoked Potential**

Chapter 1. Introduction

This chapter presents a general and brief introduction the literature that motivated the research described within this thesis. The research aims and objectives are also presented followed by a general overview of the thesis structure.

1.1. General introduction

Approximately 20-30% of the posterior region of the human cerebrum is occupied by the visual cortex (Van Essen, 2004). In macaque, more than 30 areas have been distinctly identified as being responsible for different aspects of vision (Van Essen, 2004), and it is likely that a large number of distinct visual areas also exist in the human brain (Wandell & Winawer, 2011; Weiner & Grill-Spector, 2013). It is hypothesized that these visual brain areas are organized hierarchically, whereby more complex components of the visual scene are represented at progressively higher levels of the processing hierarchy.

A dominant theory of visual processing suggests that the hierarchy of visual brain areas takes the form of two distinct streams: the dorsal and the ventral pathways (Ungerleider & Haxby, 1994). The dorsal visual stream takes an occipito-parietal route and interprets properties of a stimulus related to motion and spatial position, whereas the ventral visual stream takes an occipito-temporal route and interprets properties of a stimulus related to form, size, shape and colour. In neurologically normal observers, the two streams are interconnected and work simultaneously (Merigan & Maunsell, 1993). The early stages of each of these streams process the basic features of a stimulus and the latter stages support the integration of basic features into a complex percept. For instance, in the situation of an array of randomly moving dots, and where each dot is moving independently in relation to other dots, the motion of each dot (represented as local signals) is analysed by lower brain areas. However, in order to provide a complete coherent percept of the overall array (represented as global signals) higher-level brain areas are required.

Assessment of dorsal visual stream function is being included in a growing number of visual development studies. This is because of the theory that the dorsal visual stream is particularly vulnerable during development and therefore can be affected by perinatal risk factors as well as neurodevelopmental disorders (Guzzetta, Tinelli, & Viva, 2009; Milne & Swettenham, 2002; Pellicano, Gibson, Maybery, Durkin, & Badcock, 2005a; NM M Taylor,

Jakobson, Maurer, & Lewis, 2009). Dorsal visual stream function is often measured using motion coherence thresholds. Motion coherence thresholds assess the capacity of an individual to integrate local motion signals across the visual field into a coherent percept of global motion. This ability relies on specific dorsal extrastriate areas. Motion coherence thresholds are explained in detail in Chapter 4.

Fundamental visual functions such as visual acuity, stereopsis and motion perception each have their own developmental trajectory and take different amounts of time to reach adult levels (Braddick & Atkinson, 2011; Lewis & Maurer, 2005). Visual development relies on the maturation of neuronal circuits within the striate and extrastriate cortex (Burkhalter, Bernardo, & Charles, 1993). Part of this process involves synaptic pruning, which is most pronounced from birth until 3 years of age (Huttenlocher, de Courten, Garey, & Van der Loos, 1982). In addition, studies in humans (Noppeney, 2007) and other primates (Crair, 1998; Li, Fitzpatrick, & White, 2006) have demonstrated that visual development relies critically on early sensory experience.

The normal development of the human visual system can be affected by a variety of perinatal conditions and risk factors. Perinatal conditions such as prematurity (Birch & O'Connor, 2001), foetal alcohol syndrome (Strömland, Pinazo-Durán, Stromland, & Pinazo-Duran, 2002), hydrocephalus (Andersson et al., 2006; Guthkelch, Sclabassi, Hirsch, & Vries, 1984) and maternal drug exposure (Dominguez, 1991; McGlone et al., 2008) can affect brain function and impair visual development (Dutton & Bax, 2010). These disorders can lead to widespread visual deficits, ranging from visual processing deficits, such as impaired form perception and an abnormal motion perception threshold, to severe cortical visual impairment (Dutton & Jacobson, 2001). Another perinatal condition that has the potential to significantly affect brain function is neonatal hypoglycaemia (NH). In severe cases, neonatal hypoglycaemia can cause a pattern of brain injury that is focussed on the occipito-parietal regions of the brain that house the primary visual cortex and a number of extrastriate visual areas (Burns, Rutherford, Boardman, & Cowan, 2008; Barkovich & Ali, 1998; Filan, Inder, Cameron, Kean, & Hunt, 2006). However, the effect of neonatal hypoglycaemia on visual development in childhood is not well understood. Aside from the brain damage caused by severe hypoglycaemia, which can result in partial or complete blindness (cortical visual impairment), very little is known about the effects of mild to moderate neonatal hypoglycaemia on visual development. State-of-the-art technologies and the development of modern medicine have significantly improved the care of neonates. Neonatal abnormalities are detected early and treated efficiently. In this regard, it is reasonable to assume that most of the children who are diagnosed with NH in developed countries will only experience transient episodes of mild to moderate hypoglycaemia (Harris, Weston, & Harding, 2012).

But the potential effects of these mild to moderate episodes of hypoglycaemia on visual development is currently unknown. Understanding the long-term impact of NH on visual development is important because NH is common in children and may occur in as many as 15% (Pildes, Forbes, O'Connor, & Cornblath, 1967) of infants born full term and in up to 51% (Harris, Weston, & Harding, 2012) of the infants born at risk of NH due to conditions such as preterm birth, small for gestational age, large for gestational age, being born to diabetic mothers, as well as some congenital abnormalities.

The Children with Hypoglycaemia and their Later Development (CHYLD) study was a prospective, longitudinal study designed to observe neurodevelopmental outcomes at 2 years and 4.5 years of age in children born at risk of NH. Within the CHYLD study cohort, any children who were found to have a blood glucose level of less than 2.6mmol/L, using a heel-prick blood glucose measuring method after birth, were treated immediately (McKinlay et al., 2015). This means that most of the children experienced only mild to moderate hypoglycaemia. Therefore, the CHYLD study provided a unique opportunity to investigate the effect of NH on visual development in large group of children who experienced levels of NH that are typically observed in clinical settings. To take advantage of this opportunity, age-appropriate clinical measures of visual acuity and stereopsis, as well as psychophysical measures of global motion perception, were included in both the 2 and 4.5 year follow up assessments.

In addition to enabling an investigation into the effect of NH on visual development, the CHYLD study also allowed for more general questions relating to visual development to be addressed. Specifically, visual development from 2 to 4.5 years of age could be investigated longitudinally in a large group of children. Visual development at this stage of childhood is not well documented in the current literature, presumably due to the inherent difficulty in measuring vision in children from 2-4 years of age. In addition, due to the change in cognitive ability that occurs between 2 and 4 years of age, different age-appropriate tests are typically used for 2-year-olds than for 4-year-olds (Anstice & Thompson, 2014). For instance, preferential looking tests (Teller, McDonald, Preston, Sebris, & Dobson, 1986; D. Teller, 1979) that require much less cooperation from a child are generally used to measure vision and visual acuity in children up to 3 years of age. These tests rely on the fact that young children prefer to look at regions of a test card or computer screen that have a clearly visible image that interests them rather than a plain background. However, preferential looking tests may not measure the maximum visual function achieved by older, verbal children because their interest is not captured by images on preferential looking cards. Furthermore, tests that require active naming or matching of optotypes are more engaging and less time-consuming for older children. Therefore, as soon as children reach an age when verbal responses are

possible, tests that require naming, pointing and matching are administered (Anstice & Thompson, 2014; Dobson, Clifford-Donaldson, Miller, Garvey, & Harvey, 2009).

The necessary use of different tests at different developmental stages can complicate comparisons between measurements made at each age because it is not clear how well the results of these different tests relate to one another. It is crucial that this information is understood, not only from a research perspective, but also from a clinical perspective. In particular, clinicians commonly shift from using preferential looking tests to measure acuity at a younger age, to naming or matching tests when their patients grow older, and they may compare the results of different tests to assess factors such as treatment outcomes. Therefore, as part of this thesis, we investigated the performance of adults on a range of paediatric vision tests. Our aim was to provide new information about the aspects of vision that these tests assess and the way in which measurements of the same visual function vary across tests.

The majority of this thesis is focused on the development of vision in preschool children born at risk of neonatal hypoglycaemia. As already mentioned, vision in NH was of particular interest because visual areas in the brain (occipito-parietal) have been found to be selectively vulnerable to hypoglycaemia (Alkalay, Flores-Sarnat, Sarnat, Moser, & Simmons, 2005; Burns et al., 2008; Filan et al., 2006). We sought to plot the course of visual development from 2 years to 4.5 years in a cohort of 614 children who were born at risk of neonatal hypoglycaemia. Furthermore, using the same cohort we also sought to observe the developmental trajectory of different visual functions in children who did and did not experience hypoglycaemia at birth. The project also allowed us to explore the relationship between clinical measures of vision used at 2 years and at 4.5 years.

We were particularly interested in the development of visual acuity, stereopsis and global motion perception because these are the domains of visual function that are commonly assessed in research and that help us in understanding the relationship between vision and brain development (Uauy, Hoffman, Peirano, Birch, & Birch, 2001). We administered standard age-appropriate tasks for visual acuity and stereopsis; and for global motion perception we developed age-appropriate psychophysical methods. Specifically, an eye movement-based measure was used to measure global motion perception at 2 years (Yu et al., 2013) and a behavioural task at 4.5 years of age (these tests are described in Chapter 4). The psychophysical tasks for motion perception were modified from those used in previous published studies (Banton & Bertenthal, 1996; Narasimhan & Giaschi, 2012). In addition, standard age-appropriate developmental tests were administered to observe the

neurodevelopmental status of these children as part of the overall CHYLD study protocol (described in Chapter 3).

Visual development of the CHYLD study cohort was studies by three PhD students (including me) with their own set of unique research questions. While the other two PhD students studied the development of visual functions at 2 years and 4.5 years respectively, I studied the longitudinal development of visual functions from 2 to 4.5 years. Part of the data I present in my thesis has been published earlier (Yu et al., 2013) and also has been included in the thesis of other two PhD colleagues. My role in the study is clarified in detail within section 3.12.

1.2. Research questions

As highlighted earlier, there is a paucity of information on the development of visual functions in children from 2 years to 4.5 years. This is particularly true when age appropriate tests are used. Furthermore, the effect of low blood glucose after birth on subsequent visual development is largely unknown. Given the inadequacy of knowledge in the literature on the development of visual functions in preschool children who were born at risk of neonatal hypoglycaemia this study was designed to address following general and specific aims.

1.2.1. Overall aims

The project was designed to address two general aims:

1. To observe the longitudinal development of visual function in children born at risk of neonatal hypoglycaemia

2. To evaluate the effect of mild to moderate neonatal hypoglycaemia on visual development from 2 years of age to 4.5 years of age.

1.2.2. Specific aims

a. To assess the relationship between the results of paediatric visual acuity tests in adults who had no cognitive limitation on their performance of the tests.

Testing the visual performance of children at two different ages required the use of different age-appropriate tests. In order to assess whether the different acuity tests used at each age measured comparable visual functions, measurements were made with adult observers. Adults were chosen because they were able to complete all tests that were administered within the CHYLD study. In addition, the use of adult observers allowed us to assess the effect of optical defocus on the visual acuity tests and to compare paediatric test measurements with measurements made using the gold standard Early Treatment Diabetic Retinopathy Study (ETDRS) chart. The results of these assessments were used to inform the interpretation of longitudinal data from the CHYLD study. Specifically, these data provided an estimate of the relationships between the different acuity tests that would be expected in the absence of any influence of visual or cognitive development.

b. Are measures of visual function at age 2 years related to measures at age 4.5 years?

This aim involved the CHYLD study participants, as this cohort provided an excellent opportunity to assess the general development of the visual system in a large group of young children. Furthermore, we hoped that this aim would provide key information that could be implemented in general clinical practice while shifting from one test to another as children grow older. Data at each age were normalized to the performance of a group of visually normal adult observers to allow for an accurate comparison between the two ages.

c. Does neonatal hypoglycaemia influence the development of visual acuity, stereopsis and global motion perception?

This aim involved an investigation of the effect of the presence or absence of mild to moderate neonatal hypoglycaemia on the development of binocular visual acuity, stereopsis and global motion perception. The effect of individual and combined risk factors for neonatal hypoglycaemia was also explored.

1.3. Overview of the thesis

The overall structure of this thesis takes the form of nine chapters, including this introductory chapter. Chapter 2 begins by describing the concept of normal and abnormal visual development and draws on the literature relating to the effects of neonatal hypoglycaemia on visual development of children. Chapter 3 provides a detailed description of the design and methodology of the multidisciplinary CHYLD study of which this thesis forms a part. Chapter 4 provides a detailed description of the methods used in the research presented in this thesis. Chapter 5 deals with the validation of age-appropriate clinical vision methods used for this study. The next two chapters present the findings of the assessment of the CHYLD study participants. Chapter 6 documents the development of visual acuity, stereopsis and global motion perception from 2 to 4.5 years of age and the relationship between age-appropriate paediatric vision tests, while Chapter 7 presents results of the effect of neonatal hypoglycaemia on visual development. Chapter 8 includes a discussion of the findings of the thesis as well as the strengths and limitations. The final chapter, Chapter 9, concludes the thesis with a brief summary of the study and implications of the findings for future research and clinical practice.

Chapter 2. Literature review

This chapter provides a detailed description of previous studies relevant to this thesis. It begins with the normal development of the structure and function of human visual system. This is followed by the description of normal visual processing within the human brain. The development of visual acuity, stereopsis and global motion perception are then discussed. Finally, abnormal development is discussed with a particular focus on the concept of dorsal stream vulnerability and the effect of neonatal hypoglycaemia on visual development.

2.1. Visual development

Vision is the most richly represented sensory modality in the cortex of human and non-human primates. It is an intricate process, with many different components including visual acuity, contrast sensitivity, stereopsis, colour vision, motion perception, vernier acuity and others. These components can also be referred to as visual functions. Each of these visual functions may have their own subcomponents. For instance, visual acuity has detection acuity, resolution acuity and recognition acuity subcomponents.(Riggs, 1965) Stereopsis has coarse and fine (Shimono, 1984), and motion perception has global, local and biological subcomponents (Born & Tootell, 1992; Johansson, 1973). The most common visual functions used as outcome measures in clinical research are visual acuity and stereopsis. Motion perception and other visual functions have still not gained significance in clinical practice but there has been an increasing interest in recent years regarding the use of global motion perception tasks in characterizing the effect of ocular diseases (Bullimore, Wood, & Swenson, 1993; Shabana, Pérès, Carkeet, & Chew, 2003) and developmental disorders (Atkinson et al., 1997; Pellicano, Gibson, Maybery, Durkin, & Badcock, 2005) on the dorsal stream. Each of these visual functions has its own developmental trajectory and maturation time (Braddick & Atkinson, 2011) and may have differential vulnerability depending upon the time and type of abnormal experience affecting the visual brain areas (Taylor, Jakobson, Maurer, & Lewis, 2009).

2.2. Normal development of structures of the visual system

Human vision relies on a variety of structures. Starting from the eye and extending to the extrastriate cerebral cortex, each functional component has its own specific role. These

different structures mature in parallel and influence the development of one another. Visual experience plays a significant role in the normal development of the visual system. For instance, studies have revealed that visual deprivation at birth, via media opacities or ptosis, may lead to abnormal cortical development and eventually may result in permanent abnormal visual function. This concept was first postulated by Hubel and Wiesel (Hubel & Wiesel, 1970), where kittens were monocularly deprived of their visual experience at different ages by eye lid suturing. These kittens had considerably few binocular cells in the visual cortex and a reduced size of cells in the lateral geniculate nucleus. Disrupted visual experience early in life also causes abnormal visual cortex development in humans (Levi, 2013) and non-human primates (Lynne Kiorpes, Kiper, O'Keefe, Cavanaugh, & Movshon, 1998). This indicates that normal visual development requires appropriate development of all of the elements within the visual system along with an unobstructed visual experience.

In this section I discuss the development of normal visual structures, followed by the normal development of various visual functions. I will focus on visual acuity, stereopsis and global motion perception, as these functions are directly relevant to the empirical data reported in this thesis.

2.2.1. The eye

Structures of the eye form from different parts of the neural plate during embryogenesis (Kronfeld, 2014). The ocular structures start forming from the fifth week of gestation and then are at their respective places by three months of gestation (Kronfeld, 2014). The lens and the cornea arise from the surface ectoderm, the retina and optic nerve from the neural ectoderm, and the vasculature and sclera from the mesoderm (Kronfeld, 2014).The axial length of the human eyeball at birth is approximately 17 mm and increases at a rate of 0.16mm per week. The eyeball length reaches the adult level at around 10 to15 years of age (Scammon & Armstrong, 1925).

2.2.2. Retina

The majority of the retinal layers and synapses are already developed by the time of birth in humans. The main change that is expected to occur post-partum in the human retina is differentiation of the macular region. At birth, the human macula is very immature, without a

distinctive foveal depression, because of incomplete migration of ganglion cells and inner nuclear layers out of the foveal region (Hendrickson & Yuodelis, 1984). The fovea is immature until 15 months after birth. The structure of fovea and foveola develops to reach an adult like state within 45 months, but the length of the cone outer segments, and the cone packing density are still, at 45 months, only half that of adult values (Hendrickson & Yuodelis, 1984); however, the fovea fully matures by 10 years of age (Hendrickson, Possin, Vajzovic, & Toth, 2012).

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2.2.3 Lateral geniculate nucleus

The ganglion cells in the retina leave the eye as a bundle of fibres which form the optic nerve. These fibres project towards the brain via the optic chiasm and form a major synapse at the lateral geniculate nucleus. The lateral geniculate nucleus has two major types of cells that form six layers. These are M-cells, which form two magnocellular layers in the ventral portion of the LGN, and P-cells, which form four layers in the dorsal portion of the LGN (Garey & de Courten, 1983). M-cells form the basis of the M-pathway, which connects to the dorsal visual stream. P-cells form the basis of the P-pathway, which connects to the ventral visual stream. The function properties of these cells are described in section 2.2.3. The cells in the LGN are identifiable at birth but are immature. The difference between the immature LGN cells and adult cells is that the immature cells have an exuberance of dendrites and somatic spines. These spines decline to adult number in nine months when they reach adult level (de Courten & Garey, 1982). All of the cells in the LGN in humans reach adult size by 2 years of age (Hickey, 1977).

2.2.4. Striate cortex

In monkeys, the pattern of lamination in the striate cortex is almost adult-like at birth. However, there is some differentiation of neurons and growth of dendrites during the first few months after birth (Takashima, Chan, Becker, & Armstrong, 1980). The most striking feature in the monkey and human infant striate cortex is the presence of more spines and synapses than are present in the adult. Huttenlocher et al., (1982) demonstrated that the number of cortical synapses reaches a maximum at age 8 months after birth and reaches adult levels (60% of the density at 8 months) by 11 years. The reason for the considerable loss of synapses is still far from clear. It is thought, however, that there is pruning of unnecessary

synapses (Huttenlocher et al., 1982). It has been noted, however, that the pruning of synapses coincides with the time at which newer neuronal circuits are formed (Burkhalter et al., 1993). Furthermore, it appears that a sequential development of circuits corresponds with the development of visual function in infants (Burkhalter et al., 1993). A histological study on post-mortem human brains (Burkhalter et al., 1993) revealed that intracortical connections in the striate cortex related to the M-pathway matured earlier than the circuits for the P-pathway. Neurons in the layer 4B of the striate cortex that receive input from LGN M-cells appear to mature at 4 months postnatal age while other layers of the striate cortex, such as layer 4C that receives input from LGN P-cells, do not mature until 8 months postnatal age (Burkhalter et al., 1993).

2.2.5. Extrastriate cortex

There seems to be a hierarchical development of visual cortical neurons (Burkhalter et al., 1993) whereby neurons responsible for low-level functions mature earlier than the neurons responsible for complex functions. However, an exception to this hierarchy is the neurons in the motion sensitive middle temporal area (MT). A study on marmoset monkey brains revealed that the neurons in MT had an adult-like appearance in the first postnatal month, whereas neurons in other extrastriate areas such as areas V2, V3, V4 were just starting to develop in the third and fourth postnatal weeks (Bourne & Rosa, 2006; Bourne, Warner, & Rosa, 2005). Similar patterns of late maturation were observed in neurons of the inferior temporal cortex, where neurons start to develop only by 6 weeks postnatal age. The subsequent development of these neurons in the inferior temporal area continues over the first year of life. The same pattern seems to be consistent in humans as histochemical studies of the visual cortex have indicated early development of MT (Burkhalter et al., 1993).

2.3. Visual processing in the human brain

Visual information is transmitted from the retina to the lateral geniculate nucleus (LGN) via the optic nerve and to the primary visual cortex (Figure 1) via three distinct pathways known as the parvocellular, magnocellular (Merigan & Maunsell, 1993) and koniocellular (Casagrande, Yazar, Jones, & Ding, 2007) pathways. These pathways are very distinct in the LGN where the four dorsal layers consist of parvo-cells and the two ventral layers consist of the magno-cells. The konio-cells are laminated in-between these layers. These cells are

different morphologically as well as functionally (Irvin, Casagrande, & Norton, 1993). Physiological evidence shows that the response of cells of the M and P pathways are similar in some ways and very different in others. M-cells have large receptive fields, are sensitive to lower spatial frequencies, have higher temporal resolution and faster conduction speeds than P-cells. The function of K-cells is still unclear (Casagrande et al., 2007). Key differences between M-cells and P-cells are presented in Table 1.

Table 1 Differences between functional responses of parvocellular and magnocellular cells (Kaplan & Shapley, 1982; Nealey & Maunsell, 1994; Schiller & Malpeli, 1978; Shapley, Kaplan, & Soodak, 1981)

Parvocellular cells	**Magnocellular cells**
Sensitive to colour	Achromatic (insensitive to colour)
Highly sensitive to change in illumination	Less response to change in illumination
Slow conduction velocity	Rapid conduction velocity
Low sensitivity to low contrast	Rapidly saturating response to contrast
Rarely respond to luminance contrast <10%	Respond to contrast <2%
Small receptive fields	Large receptive fields
High spatial and low temporal frequency sensitivity	High temporal and low spatial frequency sensitivity
Higher proportion of cells in the visual system	Less proportion of cells in the visual system

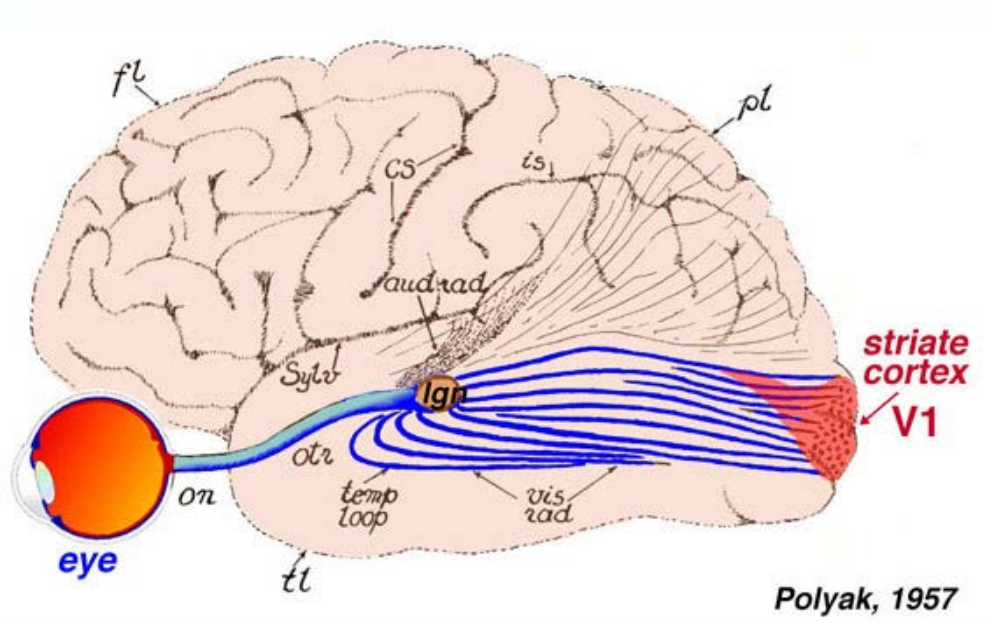

Figure 1 Simplified illustration of the visual pathway - from the eye to the primary visual cortex (V1). Axons of the retinal ganglion cells form a bundle and leave the eye as the optic nerve (on), which then synapses at the lateral geniculate nucleus (lgn). From the lateral geniculate nucleus axons project to the primary visual cortex as the optic radiations. Retrived from: http://webvision.med.utah.edu/book/part-ix-psychophysics-of-vision/the-primary-visual-cortex/

The specific characteristic functions of M-cells and P-cells contributed to speculation that the human visual system involves parallel processing streams. It has been suggested that contributions of the P and M pathways remain largely segregated from the LGN to the visual cortex so that each forms a distinct cortical pathway (Merigan & Maunsell, 1993). In the striate cortex, the P-cells terminate in 4A and 4Cβ and M-cells terminate in 4Cα layers (Figure 2).The K-cells terminate in layers 2/3 of the striate cortex (Casagrande et al., 2007). In the extrastriate cortex, the visual areas appear to be organized into two functionally specialized processing pathways, each having the striate cortex as the source of initial input (Ungerleider & Haxby, 1994). The P-pathway provides the principal information to the ventral stream via the occipito-temporal pathway, whereas the M-pathway predominantly provides input to the dorsal stream via the occipito-parietal pathway. The ventral (occipito-temporal) stream has been particularly recognized for the visual identification of objects. In contrast, the dorsal (occipito-parietal) stream has been recognized for appreciating spatial relationships among objects as well as for visual guidance of movements towards objects in space (Goodale & Milner, 1992). The ventral stream includes V1, V2, V4 and infero-temporal areas (TEO, TE) and responds to visual features relevant to object identification (colour,

shape and faces) (Allison, McCarthy, Nobre, Puce, & Belger, 1994; DeYoe et al., 1996; Puce, Allison, Gore, & McCarthy, 1995). The dorsal stream includes V1, V2, V3, V5/MT, MST, inferior parietal and supero-temporal sulcus cortex and responds features such as the location of objects and object motion (DeYoe et al., 1996; Merigan & Maunsell, 1993; Ungerleider & Haxby, 1994). The differences between these two pathways are presented in Table 2. Although these two pathways are often described as parallel processing streams, they are in fact interconnected. For example, the occipito-temporal pathway receives input from both parvo and magno pathways (Bullier, Nowak, Vision, & Lyon, 1995; Merigan & Maunsell, 1993) (Figure 3, 4). This finding has been further supported by brain stimulation and electrophysiological studies in humans (Zanon, Busan, Monti, Pizzolato, & Battaglini, 2010) and histochemical analysis of the visual cortex in mice (Wang, Sporns, & Burkhalter, 2012).

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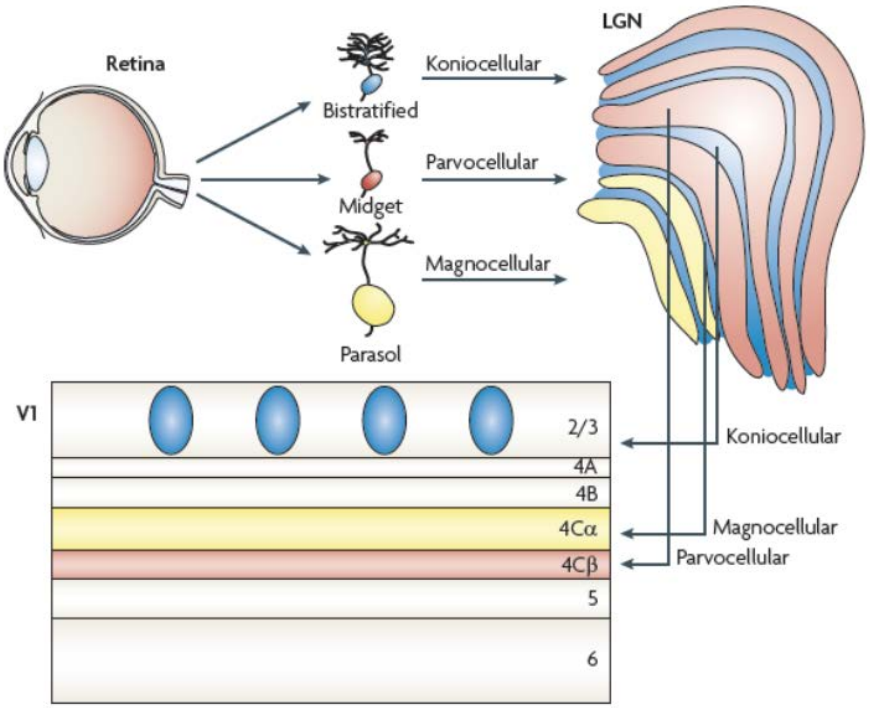

Figure 2 Parasol, midget and bistratified ganglion cells and their connection to the lateral geniculate nucleus (LGN) and into the primary visual cortex (V1). Cells from parvocellular layers of the LGN project on to the layer 4Cβ of V1 (red). Cells from magnocellular layers of the LGN project on to the layer 4Cα of V1 (yellow). The cells from the koniocellular layers of the LGN project on to the cytochrome oxidase-expressing patches (or blobs) of layer 2/3 of V1 (blue). Reprinted with permission from Macmillan Publishers Ltd: (Nature Neuroscience Reviews) (Nassi & Callaway, 2009), copyright (2002)

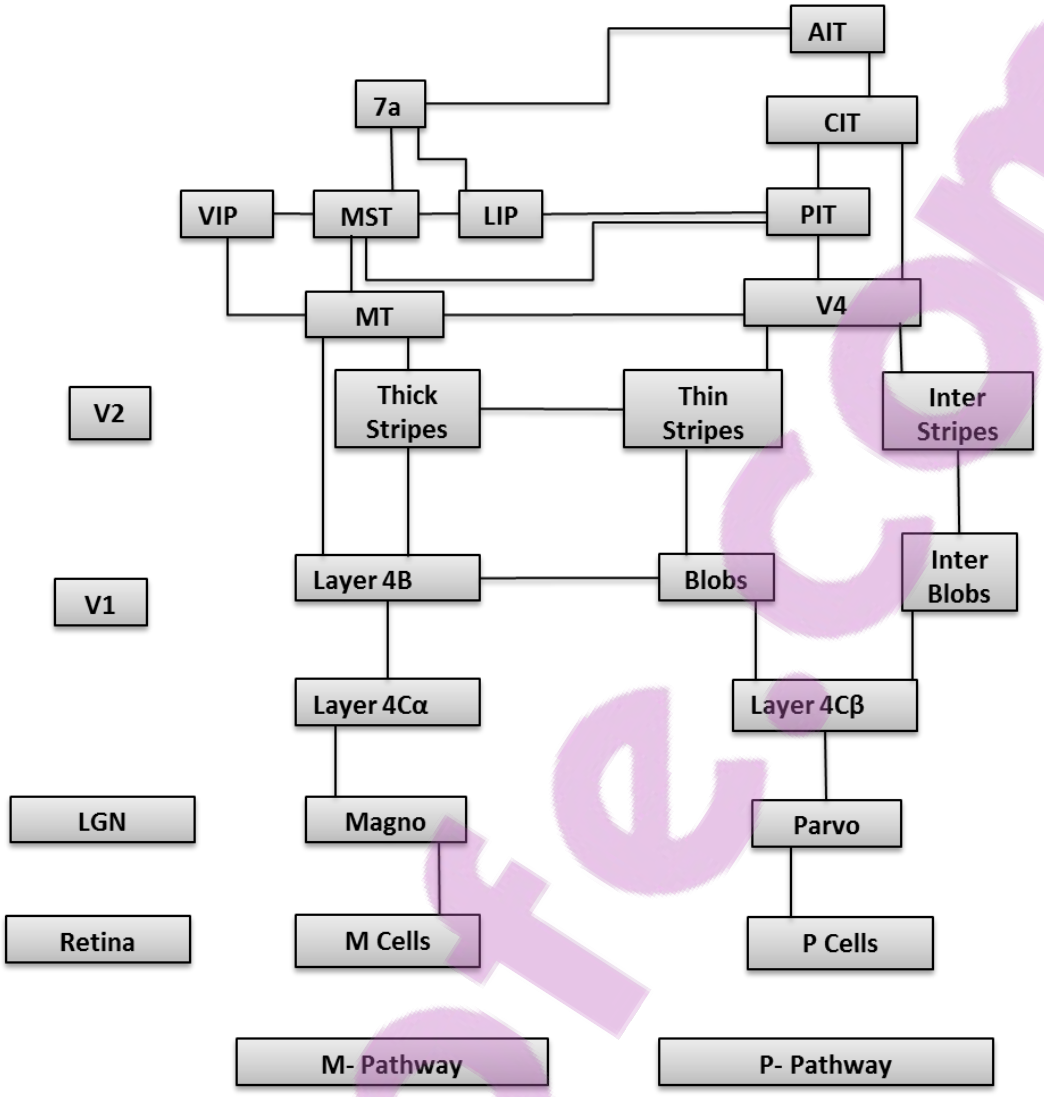

Figure 3. Connections between the ventral and dorsal pathways of the monkey brain. LGN- Lateral Geniculate Nucleus, V1- Primary visual cortex, V2- Visual area 2, Magno- Magnocellular layers of LGN, Parvo- Parvocellular layers of LGN, V4- Visual area 4, MT- Middle Temporal, PIT- Posterior Inferior Temporal area, CIT- Central Inferior Temporal area, AIT- Anterior Inferior Temporal area, VIP- Ventral Intraparietal Area, MST- Medial Superior Temporal area, LIP- Lateral Intraparietal area (Adapted from Merigan & Maunsell, 1993)

More than 30 areas in the brain are responsible for vision as shown by various anatomical and physiological studies on the monkey brain (Ungerleider & Haxby, 1994). Although there are some functional differences between visual areas of the monkey brain and human brain, several visual areas (e.g. V1, V2, V3, MT) are considered to be functionally homologous on the basis of imaging and data and assessments of patients with localized brain lesions (G. G. a Orban, Essen, Vanduffel, Van Essen, & Vanduffel, 2004).

Table 2. Differences between dorsal and ventral visual streams, MT- Middle Temporal Visual Area, MST- Medial Supero-temporal Visual Area

Dorsal Stream **(Occipito-parietal pathway)**	**Ventral Stream** **(Occipito-temporal pathway)**
V1, V2, V3, V3A, V5 (MT), MST, Infero-parietal cortex and Supero-temporal sulcus cortex	V1, V2, V4 and Infero-temporal cortex
Colour insensitive	Colour sensitive
Strongly tuning for motion direction	Weak tuning for motion direction
Weakly orientation sensitive	Strongly orientation sensitive
Sensitive to motion	Sensitive to form and shapes and colour

Visual information in the brain is processed in a hierarchical fashion such that local features are extracted at early stages of cortical processing and latter stages of processing integrate these features to form a complex representation of the visual environment. Visual processing starts from the retina via the LGN to the primary visual cortex (V1) where basic information of a stimulus, such as curvature, orientation, spatial and temporal properties, is extracted. This stage is called local processing (Hubel & Wiesel, 1968). Extrastriate cortical areas then integrate the information from V1 and extract more global aspects of an image/stimulus. With regard to the ventral stream, extrastriate visual area V2 in primates is thought to contribute to the sensitivity of complex shapes and encode complex form information. For instance, the selectivity of V2 cells for complex contour stimuli suggests that V2 cells encode information

about various aspects of object and surface boundaries. Many V2 cells are

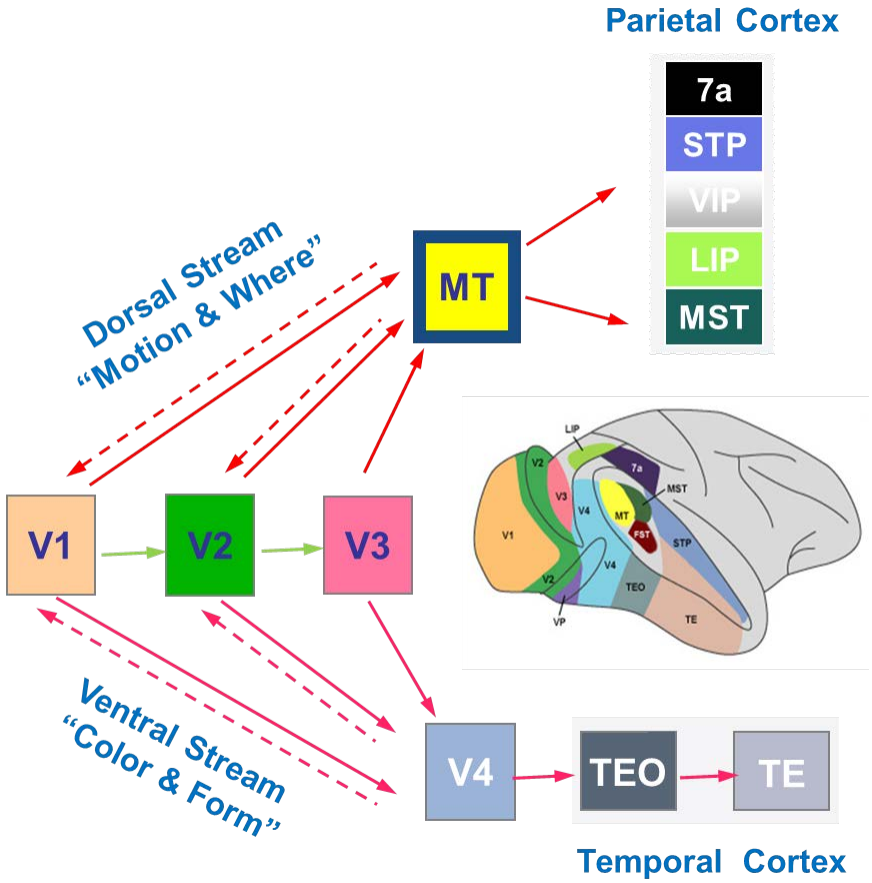

Figure 4. Diagrammatic representation of dorsal and ventral streams in the monkey brain. MT- Middle Temporal, TEO and TE- Inferior Temporal Cortex, MST- Medial Superior Temporal, VIP- Ventral Intraparietal, STP- Superior Temporal Parietal, LIP- Lateral Intraparietal, Lateral Intraparietal, 7a- Visual area 7a. Diagram courtesy of: Prof. Tatiana Pasternak, The University of Rochester.

selective for additional contour characteristics, such as the sign of curvature and/or the polarity of angles (Hegdé & Essen, 2000). V2 neurons have also been found to play an important role in analysing contours and textures and could provide useful cues for surface segmentation (Anzai et al., 2007). Another key area in the ventral stream is visual area V4, which is mostly argued for its responsibility to global form perception. This area is specifically selective to complex object features such as curved boundaries (Pasupathy & Connor, 2002). Also, the cells in V4 are particularly selective for the spatial frequency, phase, and size (Desimone & Schein, 1987; Roe et al., 2012).

In the case of motion processing, which involves the dorsal stream, V1 cells extract local motion signals that are then integrated by visual areas V3, V3A and V5 (also known as MT) . Cells in area V3 have high sensitivity to high temporal frequencies, low spatial frequencies

and low contrast thresholds (Felleman & Van Essen, 1987; Gegenfurtner, Kiper, & Levitt, 2012). Area V3 has been demonstrated to receive input from both magnocellular as well as parvocellular pathways and is, therefore, sensitive to both motion and form stimului (Lyon & Kaas, 2002). It is thought to have two halves, each reflecting the properties of the dorsal and the ventral streams(Lyon & Kaas, 2002). Adjacent to area V3 in the human brain is the visual area V3A. This area is thought to be more sensitive to motion than area V3 (Tootell et al., 1997) and to have high contrast sensitivity. The next stage of visual processing in the dorsal stream is MT or V5. This area had been established as a key region for motion processing. Even though there are multiple areas in the human brain which are sensitive to motion (Dupont, Orban, De Bruyn, Verbruggen, & Mortelmans, 1994), area V5/MT is thought to be highly responsible for a particular type of motion known as coherent or pattern motion (Braddick & O'Brien, 2001; Newsome & Pare, 1988). Despite cells which are strongly sensitive to motion and directional selectivity in area V1, there are specific properties in V5 neurons beyond that of V1 which are responsible for integration and segmentation of local information to provide a global percept. The receptive field of MT neurons is thought to be, on average, 10 times larger than that of the striate cortex (Felleman & Kaas, 1984) and these larger receptive fields support the integration of motion signals. Depending upon the complexity of the visual information, visual processing may further involve areas such as Middle Superior Temporal (MST) (Orban, Lagae, & Raiguel, 1995), Ventro Parietal (VP) and Lateral Intra Parietal (LIP) areas, as evident in the monkey brain (Maunsell & van Essen, 1983). Table 2 presents the differences between dorsal and ventral stream.

2.3.1. Summary of the visual processing of the brain

To summarize, visual information processing involves a sequential extraction of image properties at different levels of visual areas that work together to provide a complete visual percept. Information is processed in parallel streams that are specialized for form (the ventral stream) and motion (the dorsal stream) perception. These streams are interconnected.

2.4. Development of visual function

Visual functions develop considerably in the first six months of life (Dubowitz, De Vries, Mushin, & Arden, 1986). New-borns can see patterns, faces (Goren, Sarty, & Wu, 1975),

colour (Adams, Maurer, & Davis, 1986), motion (Simion, Regolin, & Bulf, 2008), and, presumably, many other visual functions which are yet to be explored. Current methods for assessing vision in infants are insufficient to determine all of the visual functions that are developed by the time a child is born. However, even with just the availability of current methods, a significant amount of literature on the development of visual function in infants has been generated. It is surprising that some of the visual functions such as biological motion perception (the ability recognise the movement patterns of other people) (Simion et al., 2008) and face perception (Goren et al., 1975) are actually quite well-developed at birth, such that they reach adult levels within a few months after birth. On the other hand, functions such as visual acuity, contrast sensitivity and global motion perception are rudimentary at birth, develop gradually, and do not attain adult levels until later in life (Leat, Yadav, & Irving, 2009; Tyler, 1990). However, the precise time course of development for each of these functions is difficult to ascertain due to differences between studies in stimulus design and psychophysical techniques. Over the years a variety of testing methods have been developed to assess vision in children. Methods have to be adapted according to children's neurocognitive development such that the maximum level of visual function attained at that age can be determined. In subsequent sections I will briefly describe common methods used to assess visual functions in children, focusing in particular on the methods used within the experiments conducted as part of this thesis.

2.4.1 Methods to assess visual function in children

Determining measures of visual function in children is a challenging task. Methods to assess visual function may need to vary for children of different ages as cognitive ability changes considerably with age and stages of development. There is a substantial amount of information regarding the development of visual function in young infants. However, information on the development of visual function in preschool aged children is scarce. This most probably is due to a lack of appropriate methodologies; in particular, psychophysical methods that are suitable for this age group of children. Tests that are commonly used in adults are not appropriate for preschool children as most of the tests are time consuming and require focused attention. They include multiple measurements with a same test and require detailed training and instruction. These procedures are tedious for children and children may easily lose interest. An ideal test that measures visual function in children should be rapid, fun and engaging. In this regard, previous researchers have applied several attempts to design tests that simulate a game platform. For instance, Abramov & Hainline,

(1984) designed a psychophysical method to determine contrast sensitivity, flicker fusion, and rod and cone function in children aged 6-8 years. They designed their tests in a simulated electronic space game platform and were successful in obtaining threshold on each of the measured function in all of the children. Similar approach has been implemented by few other researchers in determining visual acuity and stereoacuity in children. Greenwood et al., (2012) used a Pac-Man stimulus modified to resemble a Landolt-C to measure visual acuity in a group of 4-9 year old children. They also used a random dot stereogram containing pictures of ghosts from the Pac-Man game to determine stereopsis. These studies indicate that it is possible to obtain psychophysical and behavioural measures in children as young as 4 years of age. However, 'gamified' psychophysical techniques have not been attempted in children below 4 years of age.

Children aged 1 year and below tend to look at targets that are interesting to them (preferential looking) and this has been a basis of determining visual function especially visual acuity and stereopsis, in infants for many years. Preferential looking tests are widely used to determine visual acuity and have been a gold standard for assessing visual function in children. Preferential looking tests are described in sections 2.4.1.1 and 2.4.1.2.

Visual evoked potentials (VEPs) provide an objective method to assess visual functions in young children. VEPs detect electrical activity of the visual cortex in response to a visual stimulus. VEPs have been used for determining visual acuity, stereopsis and motion perception in infants.(Eileen Birch & Petrig, 1996; Bosworth & Birch, 2007; Salomão & Ejzenbaum, 2008) However, this technique requires specialist equipment, can be time consuming and is dependent on cooperation from the child.

With increasing age, cognitive and behavioural performance of children develops. Vision tests need to take these factors into account in their design in order to accurately measure vision at each age. Children aged 4 years and older are often able to perform tests that are comparable to adults (Dobson, Clifford-donaldson, Green, Miller, & Harvey, 2009; Dobson, Clifford-Donaldson, et al., 2009). However, there are no such tests that measure the best achievable visual function of children between the ages of 1 and 3 years. Hence there is very limited knowledge on how visual functions develop during that period. It is impossible to have a single test that is applicable to all ages hence new tests that are suitable to be used at this particular age and are comparable to the gold standard adult tests are required.

In subsequent sections, I will discuss currently used paediatric clinical as well as psychophysical vision tests and the principles behind them. I will also provide a discussion of the development and maturation of the visual functions that are assessed by these different tests.

2.4.1.1. Visual acuity

Visual acuity is one of the most commonly assessed visual components in determining visual function in children. Visual acuity tasks can be categorized into detection, resolution, recognition and vernier acuity. (Riggs, 1965) Tests designed on the basis of these tasks need to be administered for an individual according to their age and cognitive profile. As children may have low motivation, difficulty in understanding the task, low attention span and are distracted easily, these factors may significantly influence the measurement of visual acuity. There are various objective and subjective methods to determine visual acuity in children. The first widely accepted objective method of assessing visual acuity was the preferential looking technique developed by Davida Teller in 1986 (Teller, McDonald, Preston, Sebris, & Dobson, 1986). This method has been widely used in clinics as well as for research. This test consists of a number of cards having grating patterns of varying spatial frequency on one end and a blank grey patch on the other. The test is performed by presenting the cards to the child, who is seated comfortably on their parent's lap, facing towards the examiner (Figure 5). The threshold of acuity is determined by observing the child's eye or head movements to determine whether or not they prefer to look at the grating. No preference is interpreted as an inability to perceive the grating. The idea behind this test is that children tend to be attracted to a patterned stimulus more than a grey blank patch. This test determines the resolving capacity of a child. Though this test can be used in any age group, it is ideal for use in children below 2 years of age and who are non-verbal children with developmental disabilities and adults with multiple disabilities (Teller, McDonald, Preston, Sebris, & Dobson, 1986). Various confounding factors, such as attention of the child, inter-assessor variability, and stimulus presentation techniques, may affect the accuracy of results achieved (Clifford-Donaldson, Haynes, & Dobson, 2006; Mash, Dobson, & Carpenter, 1995), but this test has already established such a position in the visual development arena that it is considered as the gold standard for assessing acuity of infants below the age of 2 years (Beiser, Raye, & Lang, 1995; Courage & Adams, 1990; Ellis, Hartmann, Love, May, & Morgan, 1988; Preston, McDonald, Sebris, Dobson, & Teller, 1987).

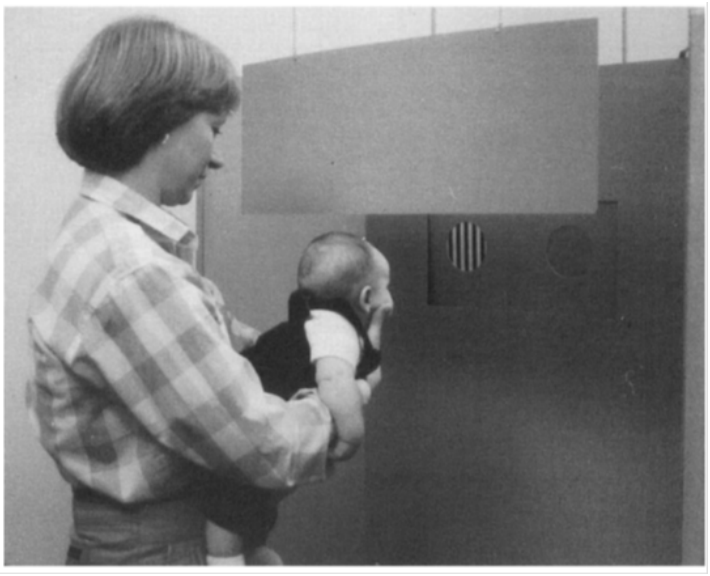

Figure 5. Performing the Teller acuity test in a child. Printed with permission from Teller et al (1986)

The use of visual evoked potentials is another objective method for assessing visual acuity in children (Dobson & Teller, 1978; Hamer, Norcia, Tyler, & Hsu-Winges, 1989; Norcia & Tyler, 1985b; Sokol, 1978). This method incorporates the use of metal electrodes that are positioned in a predetermined location on a child's head (Figure 6). Cortical responses to checkerboards or gratings with varying spatial frequency are extrapolated (Figure 6) to determine the child's visual acuity. This method is frequently used in clinical settings and/or for research purposes. It is particularly useful in situations where visual acuity needs to be assessed in children who are reluctant to engage with other tests or are too young to perform the preferential looking method. This procedure is relatively easy and requires less cooperation from the child. Despite the advantages of VEP in terms of its applicability, the comparability of this test with the preferential looking test is uncertain. A study revealed that the VEP acuity measures were better in 90% of the infants than the measures of the Teller acuity cards (Riddell et al., 1997). However, another study found that 50% of the infant measures had VEP acuity less than the preferential looking test (Katsumi, Denno, Arai, De Lopes Faria, & Hirose, 1997). Hence, it is difficult to know how well VEP responses relate to the actual percept of the infant.

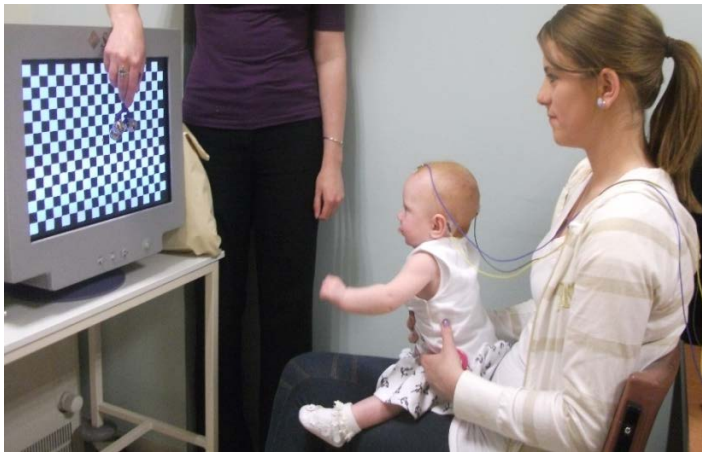

Figure 6. Pattern VEP being performed in a child Retrieved from: http://www.fphscotconf.co.uk/uploads/FPH%202012/D5/2012_11_2_laura_mcglone.pdf

As children grow older, various other visual acuity tasks such as picture matching, letter matching and vanishing optotypes can be used. None of the tasks that are currently used in children below 5 years are exactly comparable with the recognition tests used for adults.

The Cardiff Acuity Cards (CAC), a relatively new method of determining visual acuity in children has been found to be a reliable measure of visual acuity in preschool children (Adoh & Woodhouse, 1994) in terms of detecting poor visual acuity as well as having a high rate of testability. The task in this method appears to be more appealing to children than the task in the traditional Teller acuity cards and has one of the highest rates of testability in children aged 1-3 years, whereby there was 96% testability of binocular visual acuity at 1 year to 100% testability of binocular visual acuity at 3 years (Adoh & Woodhouse, 1994). The principle of this test is based on vanishing optotypes (Lars Frisén, 1986) with preferential looking techniques. This test comprises a number of rectangular neutral grey cards (a set of three at each level) with pictures of a fish, duck, car, house, train and boat on one end and blank on the other end (Figure 7).

Figure 7. Diagrammatic illustration of a child performing The Cardiff Acuity Cards. Printed with permission from Adoh & Woodhouse, 1994

The pictures are computer-generated and are drawn with a white band surrounded by a black band of half the width, on a neutral grey background; thus the average luminance of the target is equal to that of the grey background. If the target lies beyond the subject's acuity limit, it is invisible. All the pictures used are of the same overall size, but decreasing in the width of white and black bands. The acuity is determined by the narrowest white band for which the target is visible. Acuity levels range from 6/60 to 6/3.8 at one metre viewing distance, in 0.1 log steps, which gives twelve stages of acuity levels.

As children reach approximately 3 years of age, tests that require verbal or motor response such as naming shapes, matching letters can be used successfully (Becker & Hübsch, 2002). Some examples of such tests are the Lea Symbols, the Sheridan-Gardiner (SG) Test, the HOTV Chart and the Kay-Picture test, to name a few. Among the above tests, Lea symbols is the most common and is widely used to assess visual acuity in children above 3 years of age (Becker, Hübsch, Gräf, & Kaufmann, 2002), although children as young as 2.5 years have been reported to have successfully completed the test (Becker, Hübsch, Gräf, & Kaufmann, 2000). The test incorporates four shapes: house, circle, square and apple (Hyvärinen, Näsänen, & Laurinen, 1980). These shapes are different from one another only in a few defined details. Below the threshold of correct recognition, each of the four symbols appears as a blurred circle. The symbols are presented in two forms: either a single optotype or crowded optotype. Crowded optotype Lea symbols are more sensitive in detecting amblyopia (Gräf, Becker, & Kaufmann, 2000). The test procedure involves asking the child to name or match a shape on the test card that is shown by an examiner who is located at a

distance of three metres from the child. In order to match the shape which is pointed to by the examiner, the child or the caregiver is provided with a key card that consists of all of the shapes. Children above 5 years can perform gold standard acuity tests which are used in adults, such as the ETDRS and the Bailey-Lovie logMAR chart (Dobson, Clifford-donaldson, et al., 2009).

In short, it can be concluded that acuity tests need to be modified according to the cognitive and visual development of children. Even though new testing methods are emerging, in terms of applicability, Teller acuity cards dominate visual acuity measurements in infants, Cardiff Acuity Cards dominate testing in toddlers, and Lea symbols dominate testing in preschool children.

2.4.1.2 Development of Visual Acuity

Resolution Acuity

Studies implementing Teller acuity cards suggest visual acuity is poor at birth, namely, approximately 0.66 - 1 cycles/degree (Teller, McDonald, Preston, Sebris, & Dobson, 1986), but develops rapidly during the first year of life and reaches an adult level of 30 cycles/degree by 5 years of age at the latest (Beiser, Raye, & Lang, 1995; Courage & Adams, 1990; Mayer & Dobson, 1982; Salomao & Venturafx, 1995) In contrast, VEP studies demonstrate that visual acuity matures at around 6-12 months of age and does not change much after that age (Hamer et al., 1989; Norcia & Tyler, 1985a). Cross-sectional studies involving children of different ages have reported the normative values of monocular and binocular visual acuity using Teller acuity from birth to 5 years. Salomao et al. studied Teller acuity findings in 636 children of 0-36 months of low income parents and found that 1-year-old children have a mean monocular Teller acuity of 9.82 cycles per degree (approximately 6/18 Snellen acuity) which increases with age to 12.31 cycles/degree (6/14.5) in 2-year-olds and 14.98 cycles/degrees (6/12) in 3-year-olds (Salomao & Ventura, 1995). They also found that binocular acuity was slightly higher than monocular acuity in all age groups but more pronounced in 3-year-old children. A similar study by Mayer et al., (1995) in 460 children aged 1-48 months, of high- and middle-income parents, showed a fourfold increase in VA, from 6.5 cycles/degree in 1-year-olds, to 24.81 cycles/degree in 4-year-olds. These studies were in close agreement with one another.

Taken together, resolution acuity, as measured with Teller acuity cards, is very rudimentary at birth, rapidly develops in the first year of life, and then matures slowly thereafter to reach adult levels in around 3-5 years of age.

Vanishing Optotype Acuity

Adoh & Woodhouse, (1994) have published visual acuity norms of 231 children aged 12 to 36 months using the Cardiff Acuity Cards that they designed. They found that the binocular VA in log of Minimum Angle of Resolution (logMAR) increased from 0.66 at 12 months to 0.08 at 36 months and monocular acuity increased from 0.66 to 0.14. The success rate of VA assessment was 96-100% for binocular acuity and 41-91% for monocular acuity. There was a high inter-observer reliability (r=0.64 for monocular acuity and 0.72 for binocular acuity). They categorized age range of children in four groups: 12-17.9 months, 18-23.9 months, 24-29.9 months, and 30-36 months. The monocular, binocular and the range of visual acuity findings in each age group of these children is shown in Table 3.

Table 3. Median visual acuity and normal range of vanishing optotypes acuity. Adapted from: (Adoh & Woodhouse, 1994).

Age Group (months)	Monocular VA- MAR (Snellen)	Range of Monocular VA (Snellen)	Binocular VA in MAR (Snellen)	Range of Binocular VA in Snellen
12-17.9	3.9 (6/24) 0.65 logMAR	6/38 - 6/12	4.04 (6/24) 0.60 logMAR	6/48-6/12
18-23.9	2.8 (6/17) 0.44 logMAR	6/30 - 6/7.5	2.45 (6/15) 0.38 logMAR	6/24-6/7.5
24-29.9	1.97 (6/12) 0.30 logMAR	6/19 - 6/7.5	1.72 (6/10.5) 0.26 logMAR	6/15-6/7.5
30-36	1.56 (6/9.4) 0.2 logMAR	6/12 - 6/6	1.37 (6/8) 0.14 logMAR	6/12-6/6

These data suggest that monocular and binocular acuities approach adult level at around 3 years of age when measured with the CAC but continue to develop thereafter. The authors suggest that acuities within these ranges, as obtained with CAC, should be considered as normal.

Recognition Acuity

Studies consistently demonstrate that recognition acuity (assessed by an acuity task that involves pictures and letters (Atkinson & Braddick, 1983; Drover et al., 2008; Stiers, 2003) matures later than grating acuity (resolution acuity). Various authors have proposed visual acuity norms of preschool children using different tests. The commonly used tests are the HOTV, the Lea symbols, and the Landolt C chart. A study by Drover et al. to determine normative data on 373 children, using an electronic visual acuity device which presents single surrounded H, O,T,V optotypes, found that from 3 years to adulthood there was a mean improvement of 0.12 logMAR acuity (1 logMAR line) (Drover et al., 2008). The mean acuity at 3 years was 20/24 (0.08logMAR) which improved to an adult level of 20/18 (-0.04 logMAR) at the age of 6 years. Another study by Pan et al. determined the VA norms in preschool children based on 1722 black and Hispanic children (Pan et al., 2009). They included children from 30 to 72 months. They used the HOTV test as proposed by amblyopia treatment protocol (Holmes et al., 2001) and which is currently widely used for studies in preschool children both clinical and in laboratory settings. This test has been found to be effective in children as young as 2 years. They proposed VA of 20/63 (0.5 logMAR) at the age of 30-35 months, which improved to 20/32 (0.2 logMAR) at an age of 60-72 months. Inter-ocular difference was less than or equal to 0.1 logMAR in 94% of these children.

Becker et al. studied monocular acuity in 385 children aged 23 months to 70 months using Lea symbols and the Landolt C chart (Becker et al., 2002). They carried out the examinations in two different settings: first, in a paediatric general practice setting, and then they recalled the children to the hospital eye department within a month. In the paediatric practice they were able to record Lea symbols VA in 208 children. The logMAR median VA ranged from 0.2 (6/10) in children aged 23-30 months and improved to -0.20 (6/4) in the 60-70 months age group. They re-assessed (VA) in 94 previously assessed children and found that VA in a hospital setting was slightly poorer than that in the paediatric setting. This might suggest that the environment where the measurements are taken could play a role in determining the threshold of acuity measures. Pott and van Hof-van Duin, using a Rotterdam C chart (a logMAR chart having Landolt C optotypes) assessed monocular and binocular visual acuities in 201 healthy 5-year-old children (Pott & van Hof-van Duin, 1992). The binocular VA (BVA) in these children was 0.18 logMAR (6/9 Snellen) as compared to 0.1 logMAR (6/7 Snellen) in adults, which means BVA has yet to reach adult levels by 5 years on this test.

The Sonsken logMAR test (Sonksen, Wade, Proffitt, Heavens, & Salt, 2008) (a letter matching test) was used in a study to determine monocular and binocular VA norms in

children from 2 years and 9 months to 8 years. Median binocular VA was: 0.2 logMAR in a group of 2 year and 9 months children, 0.012 in 4 year-olds and -0.025 in 4.5-year-olds. The monocular median acuity in a 2 years 9 months old group was 0.25 logMAR (6/10 Snellen). It was 0.05 logMAR (6/6 $^{-2}$) in 4 year olds and 0.00 logMAR (6/6 Snellen) in both 4.5 year olds and 5 year olds. Both binocular and monocular acuities increased rapidly from 2 years 9 months to 5 years 3 months, after which there was no change.

Taken together, the studies on the development of resolution and recognition acuity suggest that grating and vanishing acuity mature earlier than recognition acuity. While most of the resolution tasks mature by the age of 5 years, recognition tasks may still continue to develop beyond that age.

2.4.1.3. Comparison between paediatric visual acuity tests

There is still a poor understanding of how measures of different paediatric visual acuity tests relate to each other. In order to obtain an accurate measure of development of visual function of a child at a particular age, tests need to be changed gradually with age; tests at a higher age require the active participation of the child and higher cognitive skills. Hence, these tests may differ in a variety of ways: optotype design, optotype sizes and testing methods. From a clinical point of view, it is very important to know the relationship between these tests as clinicians and parents are interested in monitoring the change in acuity treatment outcomes and disease progression.

Overestimation of visual acuity by the Cardiff Acuity Cards as compared to the Bailey-Lovie logMAR chart in a group comprising 21 visually normal children (mean age: 10.33 ±3.6 years) and 12 amblyopic children (mean age: 6.94 ± 1.61 years) has been reported by Geer et al. (Geer & Westall, 1996). It was revealed that the measures of the Cardiff Acuity Cards were 0.18 logMAR (nearly two lines of letters) better than the measures of the Bailey-Lovie LogMAR chart. This implies that this overestimation needs to be taken into account while interpreting data in longitudinal studies that use Cardiff Acuity Cards. Likewise, another study (Sharma et al., 2003) compared acuity measures obtained with the Teller acuity cards (TAC) and the Cardiff Acuity Cards (CAC) in a group of normal children below the age of 2 years. In the 12-24 months age group it was reported that the Cardiff Acuity Cards significantly overestimated acuity over the Teller acuity cards (mean TAC VA= 0.6 logMAR (6/24) versus mean CAC VA= 0.4 logMAR (6/15)). They further mentioned that the VA obtained with the CAC was highly variable.

In contrast, it was interesting to note that studies which have compared VA findings obtained with the Teller acuity cards and Cardiff acuity test in a deaf-blind school-aged population (Johnson & Kran, 2009) and neurologically impaired children (Mackie, Saunders, Day, Dutton, & Mcculloch, 1996) (8 months to 19 years) did not reveal a significant difference between the two tests. Similarly, studies comparing Cardiff Acuity Cards and Teller acuity in children with intellectual disabilities (Adoh, 1992) also did not report any significant differences between measures of Cardiff Acuity Cards and Teller acuity cards.

The Vision in Pre-schoolers Study (VIP study, 2003), a longitudinal study in a large cohort of preschool children, compared VA findings with the Lea Symbols test and Bailey-Lovie LogMAR chart in a clinical population aged 4.5 to 60 years. It was observed that, on average, Lea Symbols overestimated VA by one logMAR line and this difference increased as VA decreased. However, there was a high correlation between the acuity measures from these two tests and also the inter eye acuity differences, as revealed by the tests, were similar.

Another study carried out by the same Vision in Pre-schoolers Study group (VIP Study group, 2003) compared the testability and threshold visual acuity findings with HOTV and Lea Symbols in children aged between 3 and 3.5 years of age. They observed similar testability with both the tests in this group of children: 71% for HOTV and 75% for Lea symbols. However, there was a difference in threshold visual acuities with these two tests. Among the eyes that were tested with HOTV, 92% achieved monocular visual acuities of 20/50 or better; whereas, only 62% of the eyes tested with Lea symbols achieved this VA. For those eyes in which both HOTV and Lea symbols VA measures were obtained, HOTV scores showed 2.5 lines better acuities than Lea symbols. This difference in acuity findings might be due to various reasons, such as: difference in chart design, differences in mode of presentation and the attention of the children. The study concluded that the HOTV chart showed promising findings in terms of keeping children engaged with the task, which is crucial in determining threshold acuity.

In contrast to the above findings, a study on 440 children (Kvarnström & Jakobsson, 2005) that compared VA findings obtained with Lea symbols and HOTV found the average difference between Lea symbols and HOTV was just 0.01 logMAR. Though HOTV showed somewhat higher VA values, the average difference was not significant.

In summary, there are mixed findings regarding which test provides the most appropriate measure of visual acuity in a paediatric population. In normal children and adults, vanishing optotypes acuity (Cardiff Acuity Cards) appear to overestimate visual acuity (VA) in an average of 1 to 2.5 logMAR lines as compared to the Teller acuity. However, CAC provides

a consistent measure with that of Teller acuity when testing is carried out on children with neurological impairment and intellectual disorders. Letter acuity charts in the form of electronic projection, as used in Amblyopia Treatment Study protocol, provide better visual acuity than pictorial acuity cards (Lea symbols) in amblyopic as well as non-amblyopic eyes of preschool children. However, none of these tests give VA findings as exact as that of Bailey-Lovie or ETDRS LogMAR tests, which are considered as the gold standard VA tests in adults. As HOTV test and Lea symbols tests have reasonable agreement with the adult ETDRS or the Bailey-Lovie logMAR chart, current evidence suggests that they can be used interchangeably to assess visual acuity in children from 3-5 years of age. Until newer tests are available that deliver measurements that resemble those of gold standard tests, current tests such as Teller acuity cards and Cardiff Acuity Cards need to be used in children younger than 3 years.

2.5. Stereopsis

Stereopsis is a functional measure of binocularity. It provides information about the coordination between two eyes. Stereopsis is believed to have onset from 16 weeks after birth and has a rapid increase during the first year of life (Fox, Patterson, & Francis, 1986; Held, Birch, & Gwiazda, 1980) reaching one minute of arc at the age of 21 weeks (Held et al., 1980). Measures of stereopsis are of interest to scientists as it is established as a sensitive indicator for determining abnormal visual development (Birch, & Hoffman, 1992; Williams, Birch, Emmett, Northstone, & Study, 2001). Stereopsis may be hampered in a variety of visual disorders, such as anisometropia, strabismus and amblyopia (Lee & Isenberg, 2003; Rutstein & Corliss, 1999; Wallace et al., 2011).

2.5.1 Measurement of stereopsis

Several stereotests have been devised based on different principles. Similar to visual acuity tests, the tests for stereopsis are also designed differently for different age groups. Forced preferential looking (FPL) (Birch & Petrig, 1996) method is used with very young children where one part of the display consists of a stimulus contains retinal disparity and stands out of the background, whereas the other part remains flat. As children grow older, stereo tests that require more cognitive demand and involve fine measures of stereoacuity can be administered. The most commonly used commercially available clinical stereopsis tests in

young children are the Frisby stereo test and the Lang stereo tests (Lang I and Lang II), and in children over 5 years, the TNO stereo test, Randot stereo tests, Random dot E stereo test, Titmus stereo tests and the Fly stereo acuity test. The stereoacuity values in these tests range from 3000 seconds of arc to 5 seconds of arc. The Frisby stereo test is based on real depth, where the stimuli are physically separated by printing the stimuli on two sides of a glass plate, whereas the other tests either use random dot stereogram stimuli and dissociate the images between the two eyes using cylindrical lenses (Lang stereotests) or use polarization to dissociate images between the two eyes (Random dot E, Randot, Titmus, and Fly stereo test). The principle and the testing procedures of stereo tests relevant to our study are described in Chapter 4.

2.5.2. Development of Stereopsis

After the rapid development of stereopsis during the first year of life there is a gradual progression of stereo acuity until it reaches adult levels (Birch, Morale, Jeffrey, O'Connor, & Fawcett, 2005). Results are consistent in demonstrating that stereopsis continues to mature after 5 years of age (Birch et al., 2005; Ciner, Schanel-Klitsch, & Herzberg,1996) Studies that suggest stereopsis approaches adult levels much earlier have used vertical rods, contour stereograms and computer-generated dynamic random dot stimuli (Fox et al., 1986; Held et al., 1980). Therefore that threshold values for stereopsis may differ based on the type of stimuli used. The different maturation period may signify that different disparity mechanisms, such as crossed versus uncrossed, coarse versus fine, may have their own cortical pathway (Birch, Gwiazda, & Held, 1982; Leske, Birch, & Holmes, 2006; Menz & Freeman, 2003).

Ciner and colleagues (Ciner, Schanel-Klitsch, & Schieman, 1991) used the FPL method along with the computer-generated random dot targets in a group of 180 children aged 18 months to 65 months. They found that mean stereoacuity in children ranged from 250 seconds of arc in the 18-23 months age group to 60 seconds of arc in the 60-65 months age group. The adult level was 20 seconds of arc. These results suggested that stereopsis continues to develop until after 5 years of age. This study also highlighted the inherent difficulty in assessing children aged 1-3 years, as the stereo measures of children falling in this age group had the highest variability. They felt, therefore, that in addition to the developmental changes, factors relating to attention also play a significant role in obtaining threshold measures in children. Kulp & Mitchell (2005) using the Randot stereoacuity test in children aged 3-7 years of age, showed that median stereoacuity increased from 100

seconds of arc at 3 years to 40 seconds of arc at 6 years. The median threshold at 4 years was 70 seconds of arc. This finding was in close agreement with a similar study using the Randot Preschool stereoacuity test (Birch, Williams, Drover, & Fu, 2008). In this study the adult value of 30 seconds of arc was obtained by children aged 11-13 years.

A longitudinal study (Takai, Sato, Tan, & Hirai, 2005) using a computer-based random dot stereo test showed the rate of improvement in stereoacuity with age, and the findings were consistent with cross-sectional studies carried out previously. They also found that at 5 years of age children achieved a mean stereoacuity of 100 seconds of arc. Ciner et al. using computer-generated stereo smile targets along with the FPL method, measured stereoacuity in 139 children aged 6 months to 5 years (Ciner, Schanel-Klitsch, & Herzberg, 1996). The mean stereoacuity ranged from 300 seconds of arc in age 6-11 months, to 29 seconds of arc in age 60-65 months. The studies cited above come to a common corroboration that stereoacuity is not mature until at least 5 years of age. In contrast, some of the earlier studies have demonstrated that stereoacuity matures before 5 years or even as early as 6 months of age. Birch & Petrig (1996), using VEP measures, demonstrated that stereoacuity is almost adult-like (<60 seconds of arc) by 6 months of age. Similarly, Fox et al., (1986), using a three-rod test where the participants had to align a rod between two flanking rods, revealed that children aged 3-5 years had near adult stereoacuity (median: 12.6 seconds of arc). The emergence of stereopsis in infants has been found to correspond to the formation of ocular dominance columns and cells sensitive to disparity in the visual cortex. Hitchcock and Hickey (Hitchcock & Hickey, 1980) noted that ocular dominance columns were crudely developed at 4 months, whereas they were fully developed by the age of 6 months in human infants.

To sum up, stereopsis emerges at the age of 3-4 months and continues to develop until early teenage years. The maturation time, however, depends upon the type of stimuli used. Therefore, for clinical purposes, stereoacuity norms for each of the stereo tests need to be reported and the values interpreted accordingly.

2.6. Global motion perception (function of the dorsal visual stream)

Global motion perception (described briefly in Chapter 1) has been gaining popularity for its inclusion in visual development studies. The dorsal visual stream of the brain has been well recognized for this special visual function. In particular, the area V5 (MT) of human brain is part of a network of brain areas that process global motion (Tootell & Reppas, 1995). Global

motion processing requires integration of local signals into a complex global percept. For instance, the ability to detect coherently moving dots embedded in a population of randomly moving dots (a stimulus known as a random dot kinematogram) is such a function (Newsome & Pare, 1988). A motion coherence threshold, the proportion of signal (coherently moving) dots to noise (randomly moving dots) that is required for threshold detection of signal dot direction is a measure of this function. Lower the threshold, better the performance. The threshold is commonly determined using a random dot kinematogram (RDK). This method was first used by Newsome and Pare (Newsome & Pare, 1988) to observe specific motion perception deficits in macaque monkeys whose V5 was experimentally damaged. This method has been adapted by many others and has been popularized since then. The relationship between this measure and specific brain areas such as MT and V3a has been further supported by brain imaging studies in humans (Rees, Friston, & Koch, 2000) and neurophysiological studies in monkeys. (Newsome & Pare, 1988; Simoncelli, Simoncelli, Heeger, & Heeger, 1998)

2.6.1. Development of global motion perception

Studies using optokinetic nystagmus (OKN) (Banton & Bertenthal, 1996) and preferential looking (PL) (Wattam-Bell, 1996) paradigms have uncovered that global motion perception emerges in infants as young as 6 weeks (Banton & Bertenthal, 1996). There seems to be a continuous improvement in global motion perception from 11 weeks to 16 weeks using PL (70% coherence to 40% coherence) whereas the development does not progress measurably from 6 weeks to 18 weeks (36% to 37%) using PL method. Mason et al. (Mason, Braddick, & Wattam-Bell, 2003) measured global motion perception in children aged 6 to 27 weeks using both the OKN and PL. It was found that the threshold when using OKN was less dependent on age, whereas the threshold measured with PL varied significantly with age. The threshold measured with PL was always higher than that measured with OKN. The mean OKN threshold was 19.8% for the infants and 8.8% for the adults, whereas the mean threshold using PL was 54% in infants and 22% in adults. Direct comparisons between OKN and PL experiments are difficult as different stimulus parameters are required; however these studies demonstrate that OKN can be used to assess global motion perception in infants.

Knowledge about the development of global motion perception after early infancy up to at least age 3 years of age is limited. The problem appears to be common across all visual functions, namely: the difficulty in devising a testing protocol that engages children of this

age group and measures the maximum level of function attained at that age. There is a need for a longitudinal study to understand how global motion perception develops from 1 to 3 years, as this period of development has not yet been investigated.

There are no longitudinal studies in the current literature which describe how global motion processing ability in humans develops from birth to preschool age. However, cross-sectional studies involving children of various age ranges have provided some insights into maturation of global motion perception with mixed findings (Gunn et al., 2002; Parrish, Giaschi, Boden, & Dougherty, 2005). Parrish and colleagues, using the behavioural and perceptual methods, determined global motion perception in school aged children of age range 3-12 years. They reported the coherence level of 33% in 3- to 4-year-old children, which improved to 20% in 11 to 12-year-old children. The adult value using the same test was 21%. These data suggest that adult values of global motion perception are obtained at or before 11-12 years.

Likewise, a study by Gunn et al., (2002) in 368 normal children from 4 years to 11 years, showed that coherence level was 34.2 ± 11.3% in 4-year-old children, which improved to 24.9 ± 6.2% in 10- to 11-year-old children. The adult value, using the same method, was 23.5 ± 8.7%. Similar findings, that children achieved adult threshold by age 12, were reported by Hadad, Maurer, & Lewis (2011), which was further supported by a study by Narasimhan and Giaschi (2012) where they reported that motion perception was immature at least until 5-6 years of age.

However, similar to the maturation of visual acuity and stereopsis, there are discrepancies regarding the age when global motion perception attains an adult level. In contrast to the studies cited above, Ellemberg et al., (2002) and Reiss et al., (2005) did not find any differences between adult thresholds and the thresholds of normally developing 6-year-old children. These studies indicate that motion perception may reach adult levels by 5-6 years of age or even earlier. The debate mostly centres on the differences in stimuli used, as each study used different stimulus parameters.

RDKs comprise five main parameters: duration of the stimulus, dot speed, dot density, dot displacement and dot lifetime. Evidence suggests that the stimulus duration has a limited effect on maturation of global motion perception as 2000ms (Hadad et al., 2011) and 400ms (Narasimhan & Giaschi, 2012) of stimulus duration revealed consistent results. However, studies provide mixed results in maturation where different speeds are used. Using the speeds that closely resemble one another, studies have found variable results. For instance, Parrish et al., (2005) demonstrated early maturation using 1.2 degrees/sec, whereas using 1 degree/sec Narasimhan and Giaschi (2012) found delayed maturation. Similar inconsistency

has been found in studies using a speed of 18 degrees/sec (Ellemberg et al., 2002; Hadad et al., 2011).

There are studies (Arena, Hutchison, and Shimozaki, 2012; Meier & Giaschi, 2014), however, which suggest that the parameters used to generate these speeds are more important than the speed. The parameters – spatial offset and time interval of the animation frame – have been shown to play a significant role in the maturation of global motion perception. In particular, Meier & Giaschi (2014) conducted a study using different combinations of dot displacement and time interval for RDKs in a group of adults and 4 to 7-year-old children. They used two values of time interval (17ms and 50ms) and seven values for displacement (between 1 to 38 arc min) which produced a range of speeds, from 1 to 38 degrees/sec for the17ms condition to 0.3 to 13 degrees/sec for the 50ms condition. They showed that out of the seven thresholds obtained with different speeds in the 17ms condition only one condition led to the threshold that was similar in adults and children. In the 50ms condition, the children's threshold values were in close agreement with the adult threshold in four out of seven conditions. Overall, these findings imply that maturation is faster and reaches adult levels when the speed is greater than 4 degrees/sec but only when the time interval and displacements are long enough.

Based on the studies reviewed so far, there does not seem to be a concrete answer to the question of age when global motion perception reaches adult level. However, it is clear that it emerges in early infancy and continues to develop until the early teenage years. The maturation process appears to rely more on the displacement of dots rather than the speed of the dots.

2.6.2. Summary of the normal visual development

Visual acuity, stereopsis and global motion perception each have their own developmental trajectory and mature over a slightly different time course. The use of stimulus in determining these functions plays a significant role in determining their maturation time. It is possible that the same visual function may take a different course of development depending upon the method used to assess it, which implies that there might more than one pathway responsible for a single visual function. However, it is of curiosity that why infant vision is restricted to attain adult level early on. Subsequent sections will explore the probable reasons behind this discrepancy between the infant and adult vision and will also observe whether these different visual functions have a selective vulnerability during development.

2.7. Limitations on visual development

It is clear from the sections on normal visual development that different visual functions have different developmental trajectories and that some attain adult levels earlier than others. But a basic question that still remains as a matter of debate among scientists is - what are the factors that limit infants' visual performance relative to adults? There are two widely accepted views. The first view lies in the fact that infant eyes are immature in terms of their optical and photoreceptor properties. In this regard, Banks & Bennett (1988) conducted an experiment based on ideal observer analysis- a method established by Wilson S. Geisler (Geisler, 2003) where visual performance is determined in a computational approach. In this model, the optical and photoreceptor properties of the human eye established by previous anatomical studies are implemented to determine visual performance. This model provides an ideal response of an optical system without any neural noise. Banks and Bennett focused on the spatial (contrast sensitivity function, grating and vernier acuity) and chromatic visual functions and demonstrated that many of the discrepancies in performance between infants and adults could be explained due to the immaturities of the infant eye (small axial length - affects retinal image magnification) and photoreceptors (inefficient capture of photons).

Given that the human fovea continues to develop even after 4 years of age (Hendrickson et al., 2012) there could be an effect of photoreceptor immaturity on the development of visual functions until 4 years of age. In this regard, one particular study into the development of vernier acuity in children from 3 to 12 years took the concept of quantum capture into account to explain vernier acuity maturation. (Carkeet, Levi, & Manny, 1997) Based on an ideal observer analysis, the study estimated that an adult fovea captures 1.38 times more photons than that of a 45-month-old child and hence there must be an improvement of 1.08 times from the age of 45 months to adults. But the observed behavioural change was higher than the estimated factor which led the authors to conclude that concept of photon capture is not sufficient to explain vernier acuity maturation.

The second view proposes that the immaturity of the neural structures of infant visual system could be responsible for the discrepancy between infant and adult visual function. Significant neurological development occurs from infancy to adulthood. For example, there is a pruning of synapses in the visual cortex whereby the synapses decline by around 25% from 2 years of age to adulthood. (Huttenlocher et al., 1982) However, electrophysiological study of V1 neurons in normally developing infant monkeys and visually deprived monkeys shows a large discrepancy between the structural and functional development of V1 neurons and

visual behaviour. (Kiorpes & Movshon, 2004) This suggests that extra striate cortical areas play a key role in visual development.

While no studies have looked into the role of front end factors such as photoreceptor function in the maturation of stereopsis and global motion perception, it would be interesting to explore the influence of optical and photoreceptor immaturity on the development of these two visual functions and what other factors are responsible for the considerable reduction in visual performance in children as compared to adults.

2.8. Abnormal visual development

As already mentioned, normal visual development relies on the structures of the visual pathway as well as sensory visual experience. Neonatal hypoglycaemia has the potential to affect visual development (Alkalay et al., 2005; Burns et al., 2008; Vidnes & Oyasaeter, 1977) and will be a particular focus of this section of the literature review as it was a key component of the hypotheses tested within this thesis. Another focus will be global motion perception because this particular function of the dorsal stream has been shown to be particularly susceptible to risk factors for abnormal neurodevelopment (Braddick, Atkinson, & Wattam-Bell, 2003; Grinter, Maybery, & Badcock, 2010). This motivated the assessment of global motion perception in the experiments reported in this thesis. In the subsequent sections I will review a) the concept of dorsal stream vulnerability, and b) studies relating to the effect of NH and its risk factors on the development of different visual functions.

2.8.1. Vulnerability of the dorsal stream

Dorsal stream function is commonly assessed using measures of global motion perception (Grinter et al., 2010; Gunn et al., 2002). Random dot kinematogram stimuli are popular for assessing global motion perception (Grinter et al., 2010). The signal (coherent dots) to noise (random dots) ratio in this stimuli has been suggested to be a sensitive index for the dorsal stream function (Nakamura et al., 2003). Exploring the function of the dorsal stream has been of particular interest to vision scientists and clinicians in recent years. This is because, as described below, a large body of evidence has been proposed that suggests the dorsal stream is preferentially susceptible in developmental disorders (Grinter et al., 2010).

Atkinson and colleagues (Atkinson et al., 1997) first observed specific dorsal stream deficits in children with William's syndrome (WS), a neurocognitive developmental disorder. In one of their earliest studies conducted in a group of fifteen children with WS (mean age: 9.7 years), they revealed that a considerable proportion of children with WS showed a substantial and selective deficit for global motion perception as compared to control children. A subsequent study (Atkinson & Anker, 2001) supported these findings. Moreover, it has also been revealed that these deficits persist until adulthood, where adults with WS show a wider range of variability in the global motion perception compared to normal controls but are not different from controls on a test of global form perception (Atkinson, Braddick, & Rose, 2006). The authors confirm that the deficits are not due to poor understanding of the task but rather reflect differences in motion vs. form perception, as the global form and global motion tasks had very similar cognitive demands. The global motion and global form tasks used were similar to those used by Gunn et al. (2002) (described below).

To further support the claim that the dorsal stream is preferentially affected in developmental disorders, Gunn et al., (2002) conducted a study in 368 normally developed children and 24 children with hemiplegia. They used a global motion task and global form task. The global motion task involved two RDK stimuli presented simultaneously. One of these had three stripes. The two outer strips had dots moving in the opposite direction to the dots moving in the middle stripe. The other RDK had all of the dots moving in same direction. The global form task involved randomly arranged static line segments, with a selected area that formed a circle, with concentrically arranged segments. Using these stimuli they demonstrated that global motion perception was considerably poorer in children with hemiplegia, while the ventral stream remained less affected. Furthermore, they tracked the development of global form and motion in typically developing children and suggested that the development of global form and global motion is parallel throughout development, although global motion appeared to slightly lag behind global form at 6-10 years of age.

Dyslexia, another common developmental disorder, provides further support for the dorsal stream vulnerability hypothesis. Contrast sensitivity tasks have been commonly used as a measure of magnocellular function in studies involving dyslexic children (the dorsal stream receives primarily magnocellular input). Mixed results have been reported where low spatial frequency contrast sensitivity has been found to be abnormal by some researchers while others have found that it remains unaffected (Skottun, 2000; Stein, 2001). However, studies that have used global motion perception tests (Cornelissen, Richardson, Mason, Fowler, & Stein, 1995; Slaghuis & Ryan, 2000; Talcott, Hansen, Assoku, & Stein, 2000) are consistent in finding that that dyslexic children perform considerably worse than IQ and age-matched normally developing controls. Moreover, studies involving ventral stream function in dyslexia

have found that ventral stream function is relatively unaffected while comparing dyslexic children to their age-matched peers (Hansen, Stein, Orde, Winter, & Talcott, 2001; White et al., 2006). Overall, the current evidence indicates that dorsal stream is affected in this disorder.

Autism spectrum disorders (ASD) involve a myriad of disorders where children have a variety of cognitive difficulties in areas such as language, communication and social interaction. The evidence for a selective dorsal stream deficit in ASD is mixed as both dorsal (global motion) and ventral (global form) impairments have been reported (Davis, Bockbrader, Murphy, Hetrick, & O'Donnell, 2006; Sanchez-Marin & Padilla-Medina, 2008). Furthermore, the global motion deficits appear to be stimulus specific. For example, Bertone & Mottron (2003) used first-order (luminance derived) and second-order (contrast derived) global motion perception tasks and revealed that children with ASD performed similar to the normal control in the first-order task and worse in the second-order task. Nevertheless, there are studies that show that global motion perception is poor in ASD. For instance, Spencer et al., (2000) performed a study in 23 autistic children on global form and global motion perception. The global form and the motion perception task were the same as those used by Gunn et al., (2002). Children with autism performed significantly worse on the global motion task than on the global form task as compared to age-matched controls. Likewise, other studies (Milne et al., 2002; Pellicano et al., 2005; Tsermentseli, O'Brien, & Spencer, 2008) have found that global motion perception is poor in ASD. Taken together it appears reasonable to postulate that the dorsal stream is affected in these conditions.

The notion of dorsal stream vulnerability in developmental disorders is further supported by studies in Fragile X syndrome, a genetic developmental disorder characterized by poor attention, language skills and cognition. Kogan et al., conducted two studies to explore the function of the dorsal and the ventral visual streams in children with Fragile X syndrome. In addition, they also explored the function of the parvocellular and magnocellular pathways (Kogan, Bertone, & Cornish, 2004). The dorsal stream and the ventral stream functions were evaluated using the same task used by Gunn et al., (2002) whereas for the M (dorsal stream input pathway) and P (ventral stream input pathway) cell function they used flicker contrast sensitivity with variable spatial and temporal frequency. They found that both the global motion perception task and the magnocellular function task were worse in children with Fragile X as compared with their age-matched normal peers. However, they did not observe any significant difference in the global form and P-cell function task. Likewise, using first-order and second-order global motion and global form tasks, a second study (Kogan, Bertone, et al., 2004) by the same authors found that children with Fragile X syndrome differed significantly from the performance of age- and development-matched controls in

both the first- and second-order motion tasks but did not differ significantly for first-order static stimuli. Interestingly, they also found that children with Fragile X syndrome had considerably worse performance in second-order form stimuli than the age- and development-matched controls. A relatively recent study (Keri & Benedek, 2009) has looked at the function of the visual pathway using a contrast sensitivity task and vernier (alignment of objects in space) task in female Fragile X syndrome permutation carriers with normal intelligence. They provided further evidence that the magnocellular pathway is impaired (poor contrast sensitivity in low spatial frequency) while the parvocellular pathway (vernier acuity) remained unaltered, and hence proposed magnocellular defect as an endophenotypic defect in Fragile X syndrome. These findings indicate that children with Fragile X syndrome have widespread motion perception deficits, which is in favour of Braddick et al., (2003) postulation of dorsal stream vulnerability. However, it is still poorly understood whether the dorsal stream is preferentially affected.

Surprisingly, even after such an extensive advocacy regarding dorsal stream vulnerability in developmental disorders, the dorsal stream function has not been widely explored in children born with perinatal risk factors. One exception is preterm birth, where there is a reasonable amount of literature, even though studies are more in early preterm or very low birth weight children. Guzzetta et al., (2009), using a variety of global motion tasks (translational, shearing and rotational) and global form task, conducted a study in 26 school-aged children (mean age: 10.4 years) who were born preterm (<34 weeks of gestation). Out of the 26 children, 13 children had brain lesions. In comparison to full term children, preterm children performed significantly worse in all of the global motion perception tasks regardless of whether or not brain lesions were present. In contrast, performance in the global form task was poor only in children who had brain lesions. These findings highlight the importance of measuring global motion perception in detecting subtle visual processing deficits in preterm children.

Similarly, another study (MacKay et al., 2005) looked into the processing of local and global motion processing in children who had history of very low birth weight (<1500 g) at a mean age of 6 years 10 months. They used low level first-order and second-order local motion tasks and a global motion task. While comparing with full term children, it was discovered that low birth weight children were poor in all of the three motion perception tasks. Moreover, this poor performance was unrelated to the presence of any pathology (retinopathy of prematurity) or visual functional deficits, such as stereoacuity, or visual acuity deficits. This finding is in accordance with the Guzzetta et al.,(2009) study in inferring that motion perception deficits are present even in the absence of any detectable pathology or visual functional abnormality in preterm children.

Atkinson & Braddick (2007) have extensively discussed visual and visuocognitive development in preterm children from birth until school age. They have put forward a model which suggests that premature children have pervasive deficits involving global motion perception and visuospatial tasks, which could be related to dorsal cortical stream abnormality. Further evidence that preterm children (<32 weeks of gestation) have poor dorsal stream function but less affected ventral stream function is provided by Taylor et al., (2009). They implemented tasks of global form, global motion and biological motion and found that these tasks were differentially affected, whereby the global motion was highly affected, and global form was affected the least. They postulate that this could be due to a different course of maturation of these three different visual functions and which may have selective vulnerability during development.

Another perinatal condition that has recently been explored for the dorsal stream function is foetal alcohol syndrome (FAS). In a recent study (Gummel, Ygge, Benassi, & Bolzani, 2012) in children with foetal alcohol syndrome, 49 children with FAS (aged 10-16 years) were tested using multiple global motion perception tasks (150 white dots on a black background with varying signal to noise ratios) (Gummel, Ygge, Benassi, & Bolzani, 2012). The children with FAS performed significantly poorer than the controls in all of the test conditions.

To summarize, dorsal stream function appears to be substantially affected in developmental disorders such as William's syndrome, dyslexia and Fragile X syndrome. The preferential vulnerability of the dorsal stream in ASD is still under debate, even though a number of studies are in favour of this hypothesis. Perinatal conditions such as preterm birth and foetal alcohol syndrome consistently appear to have dorsal stream dysfunction regardless of brain lesions or any other pathology. Whether other perinatal risk factors or conditions, such as being large for gestational age, being the child of a diabetic mother or experiencing neonatal hypoglycaemia, reveal dorsal stream dysfunction (especially impaired global motion perception) has yet to be explored.

2.8.2. Neonatal hypoglycaemia and visual development

Newborn babies experience fluctuations in glucose metabolism ex-utero that can result in low blood glucose, a condition referred to as Neonatal Hypoglycaemia (NH). As glucose is the primary energy source (Vannucci & Vannucci, 2000) for the developing brain, any reduction in glucose availability may have significant implications for neural development. Periods of severe NH can lead to brain lesions (Barkovich et al., 1998) and there is some

evidence that milder episodes of NH may result in abnormal neurodevelopment, even in the absence of detectable damage to brain structures (Lucas, Morley, & Cole, 1988). NH is common, affecting 5-15% (Pildes et al., 1974) of newborns, with the incidence increasing to 67% (Harris et al., 2012b; Lubchenco & Bard, 1971) in children with NH risk factors. Maternal risk factors for NH include diabetes, obesity and anaemia. Risk factors relating to the neonate include being small (birth weight <10th Percentile) or large for gestational age (birth weight >90th percentile), being the smaller twin (weight difference >25%), preterm birth and congenital heart disease (Rozance & Hay, 2006). The detection and treatment of NH has been a focus of research in recent years as it is a common yet preventable disorder in neonates and which may increase in prevalence as improved perinatal medical care results in higher survival rates for children with NH risk factors (Wilson-Costello, Friedman, Minich, Fanaroff, & Hack, 2005).

It is well established that eye and visual pathway development can be adversely affected by perinatal events. For example, premature birth (Birch & O'Connor, 2001), periventricular leukomalacia (PVL – a condition where the white matter is damaged due to hypoxic ischaemic injury) (Jacobson, Ek, Fernell, Flodmark, & Broberger, 1996) and prenatal drug exposure (Dominguez, 1991) have each been linked to abnormal ocular structure and impaired cortical processing of visual information, particularly for tasks that target the dorsal visual processing stream. As mentioned in section 2.3 of this chapter the dorsal stream extends from the primary visual cortex in the occipital lobe via visual areas V3 and V5 to the posterior parietal lobe and plays a key role in motion perception, locating objects in space and enabling visual-motor coordination (Goodale & Milner, 1992). In this context, the impact of NH on visual development is of interest as it has been suggested that NH preferentially damages the occipital-parietal region of the brain (Filan, Inder, Cameron, Kean, & Hunt, 2006; Spar, Lewine, & Orrison Jr., 1994).

In this section, the current evidence linking NH to abnormal development and function of the visual pathway is summarized. I begin with a brief overview of NH from a clinical perspective and then summarize the results of studies that have addressed the effects of NH on vision, starting with the eye and progressing to visual brain areas. Finally, we review the results of a recent prospective follow-up study of infants born at risk of NH that included a detailed assessment of visual function at 2 years of age.

2.8.2.1 Clinical definition of neonatal hypoglycaemia

NH symptoms include a broad range of physiological and behavioural abnormalities that influence feeding, movement, neurological and cardiac function (Marvin Cornblath & Ichord, 2000). Therefore, diagnosis of hypoglycaemia based on symptoms alone is difficult and intermittent blood testing is typically performed if a baby is considered to be at risk of NH (Deshpande & Ward Platt, 2005).

Currently, the most widely accepted definition of a minimum safe blood glucose level for neonates is 2.6 mmol/L (Cornblath et al., 2000). While the threshold blood glucose level that requires intervention is still debated, most children are treated if their blood glucose falls below 2.6 mmol/L (Cornblath et al., 2000). Blood glucose levels of <2 mmol/L for extended periods of time have been associated with brain lesions, seizures and severe developmental disorders (Burns et al., 2008; Moore & Perlman, 1999).

2.8.2.2. Neonatal hypoglycaemia and ocular development

The anterior segment of the eye appears to be relatively robust to perinatal risk factors with the exception of prenatal exposure to alcohol (Strömland et al., 2002) (where conditions such as micro cornea, cataract, iris anomalies and endothelial abnormalities may occur), and premature birth (Cook, White, Batterbury, & Clark, 2008), where changes associated with myopia are likely. This may be why there are very few reports of anterior segment abnormalities associated with NH. The reports that do exist relate to cataract, which is consistent with a link between hypoglycaemia and cataract formation in a rat model (Chylack, 1975). In this model, hypoglycaemia was linked to low aqueous humour glucose and reduced levels of adenosine triphosphate, a coenzyme that plays a role in maintaining lens transparency. In a case series of 13 children with cataracts who had documented episodes of low blood glucose levels at different stages of development, three children had experienced NH (Merin & Crawford, 1971). However, NH does not appear to be a major cause of paediatric cataract (Pike, Jan, & Wong, 1989; Rahi & Dezateux, 2000) and a follow-up study of children with NH reported cataract in only two cases, typically following very severe, prolonged NH (Koivisto, Blanco-Sequeiros, & Krause, 2008), with the possible confounding effects of anoxia (McKinna, 1966).

Unlike anterior segment anomalies, posterior segment disorders are relatively common in children who are born with perinatal risk factors such as premature birth (Zin & Gole, 2013).

Optic nerve hypoplasia is the posterior segment disorder most commonly associated with NH. In one of the first studies of visual outcomes following NH, McKinna (1966) reported that 7 out of 17 babies (41%) who experienced severe NH had evidence of optic nerve hypoplasia in addition to symptoms indicative of widespread brain injury. Similarly, Fahnehjelm et al. found that 12 out of 28 children (43%) with optic nerve hypoplasia had experienced NH (Fahnehjelm, Fischler, Jacobson, & Nemeth, 2003). However, a larger study conducted to determine the causes of optic nerve hypoplasia revealed that only 6 out of 51 (12%) children with optic nerve hypoplasia had experienced NH (Margalith, Jan, McCormick, Tze, & Lapointe, 1984). To place this association in context, 43% of the children with optic nerve hypoplasia experienced no problems during the perinatal period. The pathogenesis of optic nerve hypoplasia is unclear; however, it is believed to be due to a failure of the retinal ganglion cell layer to differentiate normally, which is most likely to occur in utero (Frisén & Holmegaard, 1978). Interestingly, one study has reported a higher prevalence of optic nerve hypoplasia in children of diabetic mothers (17 out of 93 patients), which the authors concluded was due to partial failure of ocular development in a diabetic intrauterine environment (Petersen & Walton, 1977). The increased risk of optic nerve hypoplasia, therefore, may be more directly related to the maternal risk factors for NH, rather than a result of fluctuations in blood glucose levels post-partum. Macular hypoplasia (Tam et al., 2008) and bilateral optic atrophy (Yalnizoglu, Haliloglu, Turanli, Cila, & Topcu, 2007) have also been reported in children with NH. These babies, however, had a range of comorbid conditions, including a genetic abnormality, sepsis and hyperbilirubinemia, making it unlikely that NH was the primary contributing factor.

In summary, NH does not seem to significantly influence development of the eye, retina or optic nerve. However, the potential association between severe NH and optic nerve hypoplasia warrants further investigation.

2.8.2.3. Neonatal hypoglycaemia and refractive error

The refractive status of children with a history of NH has been described by two studies. Koivisto et al.,(2008) found high myopia in one child and high hyperopia in another within a group of 151 children who experienced NH. Karimzadeh et al. found a higher proportion of children with refractive error, whereby 6 out of 27 children with NH (mean age: 3.5 years) had significant refractive errors (Karimzadeh, Tabarestani, & Ghofrani, 2011). However, the 22% rate of significant refractive errors reported by the Karimzadeh et al. study was only slightly above the upper estimate of 18% within the general population of children of a

comparable age (O'Donoghue et al., 2011). The development of refractive error is regulated by an active visually guided feedback loop (emmetropization) whereby local ocular signals match the axial length of the eye to its optical power (Wildsoet, 1997). There is no evidence that NH would disrupt the emmetropization system, particularly as an intact visual (eye-brain) pathway is not required for regulation of refractive error (Wildsoet, 2003).

2.8.2.4. Neonatal hypoglycaemia and binocular vision

Three studies have indicated a possible association between NH and strabismus. Yalnizoglu et al., (2007) found that alternating exotropia was present in 1 out of 13 (8%) of children with a history NH, and Murakami et al., (1999) reported strabismus (type unspecified) in 1 out of 8 cases (13%). In a larger study, Koivisto et al., (1972) reported strabismus in 9 out of 144 (8%) of infants with a history of NH. However, this rate of strabismus was comparable to that present in their non-hypoglycaemic control group (3 out of 54, or 6%), suggesting that NH may not have been an important contributing factor to the presence of strabismus in their cohort. Clear links between patterns of brain injury and the presence of strabismus have not been found in studies that have included brain imaging (Burns et al., 2008; Murakami et al., 1999). This may suggest that strabismus is not associated with brain injury caused by NH, or that NH can damage brain areas involved in binocular visual development in a way that is not evident on MR images, or that strabismus is unrelated to NH. Nystagmus has also been reported in a small number of infants with a history of NH (Koivisto et al., 2008; Murakami et al., 1999). However, as with strabismus, a direct link with NH is uncertain.

2.8.2.5. Neonatal hypoglycaemia and cortical processing of visual information

Severe and prolonged NH can result in ischemic and atrophic brain injury, affecting the cortex and underlying white matter (Burns et al., 2008). A number of case and retrospective cohort studies involving brain imaging have suggested that the occipital and posterior parietal lobes are particularly susceptible to brain injury caused by NH (Barkovich & Ali, 1998; Filan et al., 2006; Tam et al., 2008). For example, NH was identified as the most common cause of brain injury in a group of 21 infants with occipital lobe abnormalities (Wang et al., 2012). The reason for the posterior pattern of brain injury induced by NH is unknown. However, this is of particular interest with regard to vision because visual brain areas are concentrated within the occipital lobe and extend anteriorly to the parietal and

temporal lobes. Injury of the optic radiations following NH has also been reported (Filan et al., 2006) with clear implications for visual processing. Notably, the theory that NH causes localized damage to posterior brain areas was not supported by a relatively large retrospective cohort study, which reported diffuse, widespread injuries evident on MR images obtained up to six weeks after birth. However, 29% of the cases reported in this study did exhibit a posterior pattern of brain injury, compared to only 6% with an anterior pattern. Furthermore, it appears a posterior pattern of brain injury does not occur if NH occurs in conjunction with hypoxia-ischemia (Tam, Haeusslein, & Bonifacio, 2012) and, therefore, comorbidities are likely to influence the pattern of brain injury observed across different studies.

As might be expected from the at least partial vulnerability of visual brain areas to NH, visual impairments characteristic of abnormal cortical processing have been reported in babies and children who experienced severe or recurrent NH (Alkalay et al., 2005; Karimzadeh et al., 2011). In one of the most detailed studies of the associations between brain injury and NH to date, Tam et al. (Tam et al., 2008) conducted a retrospective case review of infants who had experienced NH and had also undergone diffusion-weighted brain imaging. Of the 18 infants for whom follow-up data were available, 2 (11%) were classified as having cortical visual loss when assessed at 4-8 months corrected age. One was diagnosed with cortical blindness indicative of bilateral occipital lobe injury and the other with homonymous hemianopia indicating a unilateral injury. Importantly, only infants who experienced NH for two days or more were subsequently diagnosed with cortical vision loss. Visual evoked potentials were also measured in 20 of the infants, with abnormal VEPs reported in 11 children (55%). Details of the VEP protocol were not provided; however, it is interesting to note that there were no strong relationships between VEP findings, visual outcomes and occipital lobe diffusion measures. Occipital lobe diffusion restriction was apparent for 8 out of 45 (18%) infants assessed. These eight infants all underwent diffusion imaging within six days of NH and were born at term. No occipital lobe diffusion restriction was observed in babies who were imaged six days or more after experiencing NH or in babies born preterm.

The absence of a direct relationship between patterns of occipital lobe brain injury and visual deficits is also evident in a number of smaller case series and retrospective case reviews involving infants with NH. For example, Murakami et al., (1999) found that 7 out of 8 infants and children who had experienced NH exhibited parieto-occipital lobe injuries, although only 3 out of 8 developed impaired visual acuity. Similarly, Filan et al.,(2006) reported occipital brain injury in all four cases of NH studied. However, only one infant exhibited a visual impairment. Burns et al.,(2008) found a reasonably consistent relationship between posterior brain injury and visual deficits (11 out of 35) in their cohort. They mention, however, that

some infants with severe occipital injuries did not show signs of visual deficits. Finally, Yalnizoglu et al., (2007) studied 13 children with a history of NH and showed that 10 infants had either occipital or occipito-parietal brain injury but only four of them developed visual impairment.

At least three non-mutually exclusive explanations could account for the dissociation between posterior brain injury and visual deficits in studies of infants who experienced NH. Firstly, although the methods used for visual assessment are typically not described in papers dealing with NH, the testing was often conducted at a young age when accurate assessment of visual function is extremely challenging (Trager et al., 2009). Hu et al., (2014) demonstrated that even VEP measurements are challenging to interpret in neonates, as although all infants (15 out of 15) with NH and posterior brain injury had abnormal VEP waveforms, 6 out of 11 healthy control infants also had abnormal VEP findings. Due to the difficulty in measuring visual function in infants, higher-level deficits such as agnosias resulting from damage to extrastriate brain areas as well as more subtle visual field or spatial or temporal contrast sensitivity losses may not have been evident in previous studies. Providing some support for this idea are studies demonstrating that experimentally induced hypoglycaemia in healthy adults does not affect clinical measures of visual acuity or stereopsis, but does impact on spatial contrast sensitivity and neuropsychological tests targeting higher-level visual processing and attention (inspection time, change detection and movement detection) (McCrimmon, Deary, Huntly, MacLeod, & Frier, 1996).

Secondly, NH causes brain injury early in life and the visual cortex is highly plastic during infancy and early childhood. It is conceivable that neural plasticity allows the remaining visual areas to compensate for those damaged by NH (Guzzetta et al., 2010; Slotnick, Moo, Krauss, & Jr, 2002; Werth, 2006). Furthermore, both diffusion and structural MR data suggest that recovery of occipital regions is possible weeks or months after NH, indicating that NH may not permanently damage the occipital lobe in all cases (Kinnala, Rikalainen, & Lapinleimu, 1999; Tam et al., 2008).

Thirdly, deficits in vision resulting from early disruption to the visual system may not become apparent until later in development. For example, delayed effects of early and brief visual deprivation have been reported for abilities such as face perception and are referred to as ‘sleeper effects’ (Maurer, Mondloch, & Lewis, 2007). It is not known whether abnormal visual cortex function early in development can result in a similar pattern of abnormal visual development later in life.

2.8.2.6. Mild to moderate neonatal hypoglycaemia and vision

The majority of the studies described above have used retrospective case series designs to investigate the effect of severe or prolonged NH on the eye and brain. However, a recent prospective follow-up study of children born at risk of NH, the Children with Hypoglycaemia and their Later Development (CHYLD) Study (McKinlay et al., 2015), has provided new data on the effects of mild to moderate, successfully treated NH on visual development. The CHYLD study, of which this thesis is part followed up 404 two-year-old infants born at risk of NH and included a thorough optometric vision screening (visual acuity, stereopsis, ocular health, motility, refractive error) and a measurement of global motion perception, a function of the dorsal visual stream, as part of the assessment protocol. Two composite scores were generated, relating specifically to vision. The first was a vision impairment score that captured problems with ocular health, eye alignment (strabismus), eye movements, stereopsis and visual acuity. The second was a refractive error score that captured clinically significant refractive error. Global motion perception was measured using motion coherence task, which assessed the ability to tolerate noise in an otherwise coherently moving dot field (a motion coherence threshold). Eye movements were used to judge whether the child could perceive the coherent motion.

Of the 404 children assessed, 216 experienced mild to moderate NH, which was quickly treated. No differences in vision impairment, refractive error or global motion perception were found between the children who did and did not experience NH (See Table 4), suggesting that short periods of mild to moderate NH do not affect visual development at age 2 years. Longitudinal development of these visual functions until 4.5 years will be presented in this thesis.

Table 4. Vision outcomes from the CHYLD study, data from (McKinlay et al., 2015). Results are shown for the main vision outcomes: global motion perception (motion coherence threshold in units of % signal), visual impairment and refractive error. Larger values on each measure indicate a poorer outcome.

Outcome	Hypoglycaemia N=216		No Hypoglycaemia N=188		Adjusted mean difference or risk ratio (95% CI)	P
Motion coherence threshold, mean % (SD)	41.5 (14.2)	204	43.2 (13.4)	175	-1.7 (-4.5, 1.1)	0.24
Vision impairment score, n (%)		215		186	1.11 (0.76, 1.62)	0.58
1	48 (22)		29 (16)			
2	6 (3)		10 (5)			
3	1 (1)		1 (1)			
Refractive error score, n (%)	8 (7)	113	10 (11)	93	0.64 (0.28, 1.50)	0.31
1	1 (1)		0 (0)			
2	0 (0)		1 (1)			
3						

Current evidence suggests that severe and prolonged NH can injure brain areas involved in visual processing, although the effect of these injuries on later visual function is currently unknown. There are no consistently reported effects of severe NH on ocular development or eye alignment. Brief and treated mild-to-moderate NH does not appear to affect visual function at 2 years of age (McKinlay et al., 2015). However, the effects of abnormal visual experience early in life may only become apparent in late to middle childhood. It remains to be seen whether NH has an impact on visual function later in development.

2.9 Summary of the literature review:

Visual processing is a complex process that involves structures extending from the eye to the brain. The visual system is functionally divided into two distinct streams- the dorsal stream and the ventral stream. The dorsal stream is responsible for visually guided action whereas the ventral stream is responsible for object recognition. These two pathways are interconnected in the normal visual system.

Infant's visual abilities are crude at birth and gradually mature with increasing age. Various methodological approaches need to be applied in order to extract information regarding visual development from young children. The maturation time of different visual functions varies. Part of this variation may be due to the visual tests that are available for use with children. While visual acuity and stereopsis mature at earlier ages, global motion perception has a long trajectory for maturation. There is a considerable amount of knowledge regarding the development of visual function from 0 to 12 months of age but the literature regarding the development of visual function from 1 to 3 years is inadequate. This may be partly due to the lack of suitable tests that are applicable to this age group of children. Use of age appropriate tests is unavoidable in understanding development of best achievable visual function of children at each age. While use of age appropriate tests for longitudinal studies complicates comparisons between measurements made at different ages, the normalization of child thresholds relative to adult adults can address this issue. Determining the age at which a child's performance reach half the adult level is also a technique for comparing data across different ages.

There is a relatively large body of evidence that suggests the dorsal visual stream is preferentially affected in developmental disorders such as autism, William's syndrome, cerebral palsy, dyslexia and foetal alcohol syndrome. There is some evidence that preterm birth may also lead to abnormal dorsal stream function. It is possible that any condition that affects parieto-occipital region of the brain may be associated with dorsal stream dysfunction.

Neonatal Hypoglycaemia causes a myriad of ocular and visual disorders such as strabismus, nystagmus, and cortical visual impairment. Severe NH preferentially affects the parieto-occipital region of the brain, the region of the brain that houses the visual areas that are primarily responsible for visually guided action. Hence, it is possible that dorsal stream function is affected in NH. Most of the literature has been focused on the effects of severe NH. The effect of mild to moderate hypoglycaemia on long term neurodevelopment is not well understood.

The research described in this thesis observes the development of three visual functions in children from 2 years to 4.5 years of age. The research described in this thesis uses a the normalisation of child thresholds to adult to understand the effect of mild to moderate neonatal hypoglycaemia on the longitudinal development of visual acuity, stereopsis and global motion perception from 2 to 4.5 years of age.

Chapter 3.The Children with Hypoglycaemia and their Later Development (CHYLD) Study

This chapter provides an overview of the CHYLD study of which the research described in this thesis was part. Methodological details relating to the design of the CHYLD study are also provided.

3.1. Introduction

The CHYLD study was a large multidisciplinary prospective cohort study investigating the development of young children who were born at risk of developing neonatal hypoglycaemia. The cohort of 614 children was recruited as part of two studies: The Babies and Blood Sugar's Influence on Electroencephalography Study (BABIES) (Harris et al., 2011) and the Sugar Babies Study both carried out at Waikato Hospital, Hamilton, New Zealand. The BABIES Study was primarily aimed at determining the relationship between brain function as measured with EEG and blood glucose level in children born at risk of neonatal hypoglycaemia (NH) (N=104). The Sugar Babies Study (Harris, Weston, Signal, Chase, & Harding, 2014) was a randomized clinical trial primarily aimed at evaluating the effect of 40% dextrose gel in reversing neonatal hypoglycaemia, which was detected by heel prick in the first 48 hours of life (N= 512). Two children were enrolled in both studies so the total number of participants in the CHYLD cohort was 614 (104+512-2). In addition to the standard heel-prick testing for blood glucose, the babies in the Sugar Babies study also wore interstitial glucose monitors, which provided continuous measurements of blood glucose for up to seven days after birth. The data from the continuous monitors were analysed after the trial was complete and demonstrated that many of these children experienced hypoglycaemic episodes that were not detected by standard heel-prick testing and, therefore, were not treated (McKinley et al., 2015). The CHYLD study team assessed cognitive and physical development, memory, vision and the general health of these children at 2 and 4.5 years of age and related these outcomes to the periods of hypoglycaemia that many of them experienced as newborns.

For the purpose of this thesis, only heel-prick blood glucose levels were considered for analysis, as this is the current standard clinical method. Glucose level of less than 2.6mmol/L (Cornblath et al., 2000) during the first week after birth was considered as neonatal hypoglycaemia. Any children who were detected as having neonatal hypoglycaemia underwent immediate treatment based on current clinical practice guidelines.

3.2. Objectives of the CHYLD study

The main objective of the CHYLD study was to observe neurodevelopment of children born at risk of having low blood sugar at birth and to relate the developmental outcomes with blood sugar levels in the neonatal period obtained via two measurement methods: the heel-prick method, and continuous blood glucose monitoring, a novel method not previously used in newborns.

It should be noted that these CHYLD study objectives are not the main objectives of this thesis. The objectives relevant to this thesis are explained in the earlier sections 1.2.1 and 1.2.2.

3.3. Study design

The CHYLD study was a longitudinal, investigator-masked observational study of children who were born at risk of having episodes of NH. As mentioned in section 3.1, these children were recruited at birth for two different studies and then followed-up until 4.5 years. The first neurodevelopmental follow-up was performed at the corrected age of 24 ±1 months. The second neurodevelopmental follow-up was conducted as the corrected age of 54 ± 2 months.

The age of 24 months for the first follow-up was chosen based on the consensus that children have developed cognitive and motor skills that are able to be evaluated via validated standard tools and by this age perinatal events still have influence on their development. The second follow-up at 54 months provided an opportunity to reassess physical, cognitive, motor and visual development directly, before the children had started school. Longitudinal assessments at a later age may become more complex once children have started school because specialized educational or health support may be made available to some children and not others. Also, by 54 months children develop independent behaviours that require a higher level of cognition, collectively known as executive functions.

3.4 Rationale for including visual assessment component in the CHYLD study

It is evident from Chapter 1 and Chapter 2 that children exposed to severe neonatal hypoglycaemia have a myriad of visual abnormalities such as strabismus, nystagmus. Furthermore, most of the imaging studies have come to a common ground that NH preferentially targets the occipito parietal region of the brain. This region of the brain represents the dorsal visual stream of human visual pathway. Hence, in order to explore the

effect of NH on visual brain areas (particularly the function of the dorsal visual stream), global motion perception test, a test that has been shown to target the dorsal visual stream function was implemented. And to screen children for any vision disorders early in life, the common clinical vision tests were implemented.

3.5. Methods used for the CHYLD study

The children enrolled for the CHYLD study had heel-prick and continuous blood glucose monitoring methods available, which provided glucose level data at the time of birth. The heel-prick blood glucose level was measured one hour after birth and then every 2 to 4 hours before feeding and up to 12 hours, and as required thereafter. Continuous glucose monitoring was conducted by inserting a sensor into the lateral aspect of the thigh. The sensor was kept there for a minimum of 48 hours and a maximum of up to 7 days.

At follow-up age, the children underwent a series of neurodevelopmental assessments, including vision. Details of the methods used for neurodevelopmental assessment for this study are presented in section 4.1.2 and 4.2.6.

3.6. Participants of the CHYLD study

Six hundred and fourteen infants from the BABIES and Sugar Babies studies were eligible to be enrolled in the CHYLD study. For the two “feeder” studies, mothers of the babies who were at risk of having NH were identified before the babies were born and were recruited for the study. Risk factors for having episodes of NH were:

- Small for gestational age (birth weight <10th percentile or < 2500g)
- Large for gestational age (birth weight >10th percentile or >4500g)
- Born to diabetic mothers
- Not feeding well
- Stressed: infants with congenital heart defects, respiratory distress, sepsis, haemolytic disease
- Born late preterm (≥32 weeks and ≤37 weeks of gestation).

Babies were not included if they had:

- Congenital malformations that were severe in nature
- Terminal illness
- Skin lesions that prevented application of the sensor used for continuous glucose monitoring.

If a child had more than one risk factor the primary risk factor was determined based on priority as follows: born to diabetic mothers, preterm, small for gestational age, large for gestational age and others.

Children who had acquired brain injury after the neonatal period were not included in the follow-up study.

3.7. Participants included in the analyses of this thesis

Out of 614 children eligible at the time of recruitment, 406 (77%) were followed up at 2 years. Out of the 406 assessed at 2 years, 95% (385) completed all the neurodevelopmental assessments, and 99% (405) completed vision assessments. Of the total 406 children assessed at age 2 years, 355 (87%) were assessed again at age 4.5 years. Hence, this thesis is based on the data of 355 children who were assessed both at age 2 years and age 4.5 years.

3.8. Ethics approval

The CHYLD study 2-year follow-up received ethics approval from the Northern Y Health and Disability Ethics Committee (NTY/10/03/021) of the Ministry of Health. To extend the study for the 4.5-year follow-up, an amendment was submitted, which was approved by the same ethics committee on the 24th of June 2011.

3.9. Consent process

During the recruitment processes for the BABIES and Sugar Babies neonatal studies, parents were informed about the possibility of following up these children in their later years. For the 2-year follow-up study, a set of documents that included an invitation to participate in the CHYLD study was sent to all families involved in the two earlier studies as their children approached two years of age. A further set of documents containing detailed information regarding the CHYLD study was provided to those families who agreed to take part. Finally, informed written consent was provided by the parent/caregiver on the date of the assessment. The same process used for the 2-year follow-up was done for the 4.5-year follow-up.

3.10. Venue of the assessments

Most of the 2-year follow-up assessments were conducted either at a local hospital or at a research house in Hamilton, Waikato, New Zealand. The research house was specifically established as a dedicated facility for assessing these children. In some cases, where the family was unable to attend any of these venues, assessments were conducted either in their own homes or at a community childhood centre (for example, Plunket) near to the family's location. Most of the assessments at 4.5 years were carried out at the research house in Hamilton. However, as with some of the 2-year-olds, assessments at 4.5 years were carried out at different locations depending upon the location of the family.

3.11. Child Assessors

Neurodevelopmental assessment was carried out either by registered New Zealand psychologists or research nurses. Vision assessments were carried out either by New Zealand registered optometrists or optometrically trained PhD students who were not registered in New Zealand but who were credentialed for the vision assessment procedures. The general health/paediatric assessment was carried out by qualified paediatricians or credentialed medical students. All assessors were provided with dedicated training specifically for the study. Good Clinical Practice training was completed by all of the assessors involved in the study. The tenets of the Declaration of Helsinki were followed while assessing the children.

3.12. The role of the author in the CHYLD study

I am an optometrist with an overseas qualification. I was credentialed for vision assessment procedures by registered New Zealand optometrists who were my associate supervisors for this project. The methodology for the CHYLD 2-year-old study had already been designed by the CHYLD steering committee (a committee that represented neonatologists, vision scientists, optometrists and psychologists) before I enrolled into the PhD program. The CHYLD study was already recruiting 2-year-old participants and had completed data collection in almost 50% of the children.

Originally, the CHYLD study was designed as two cross-sectional studies with the primary aim of observing neurodevelopmental outcomes at 2 years and 4.5 years of age in children born at risk of neonatal hypoglycaemia. Hence, the methods chosen at each age group were optimised to detect developmental deficits at each age. Neurodevelopmental tests along with the vision tests were selected based on their robustness and high testability in that particular

age group of children. Some children missed the assessments at 2 years because they were outside of the age window when the CHYLD study began. However the missed children were assessed at age 4.5 years. Hence, the number of children assessed at 4.5 years was greater than at 2 years. It is of particular importance that the majority of the children were assessed both at 2 years and 4.5 years.

The study of cross-sectional visual development at 2 years and 4.5 years was conducted separately by other 2 PhD students. My role in the CHYLD study was to extract the information from these two cross-sectional studies and provide longitudinal information. As different methodological approaches were used to assess visual functions at 2 years and 4.5 years, I devised a technique that allowed me to quantify the developmental change from 2 years to 4.5 years of age. In addition, using this technique, I was able to show the effect of neonatal hypoglycaemia on the longitudinal development of visual functions. I also conducted vision assessments in 2-year-old children and followed up the same children at 4.5 years of age. I collected data on approximately 30% of the 2-year-old children and 60% of 4.5 year old children. In addition, I designed research questions specific to my project, (described in section 1.2.1 and 1.2.2) and performed the statistical analyses required for my project. The synopsis of my role within and besides the CHYLD study is illustrated in Figure 8.

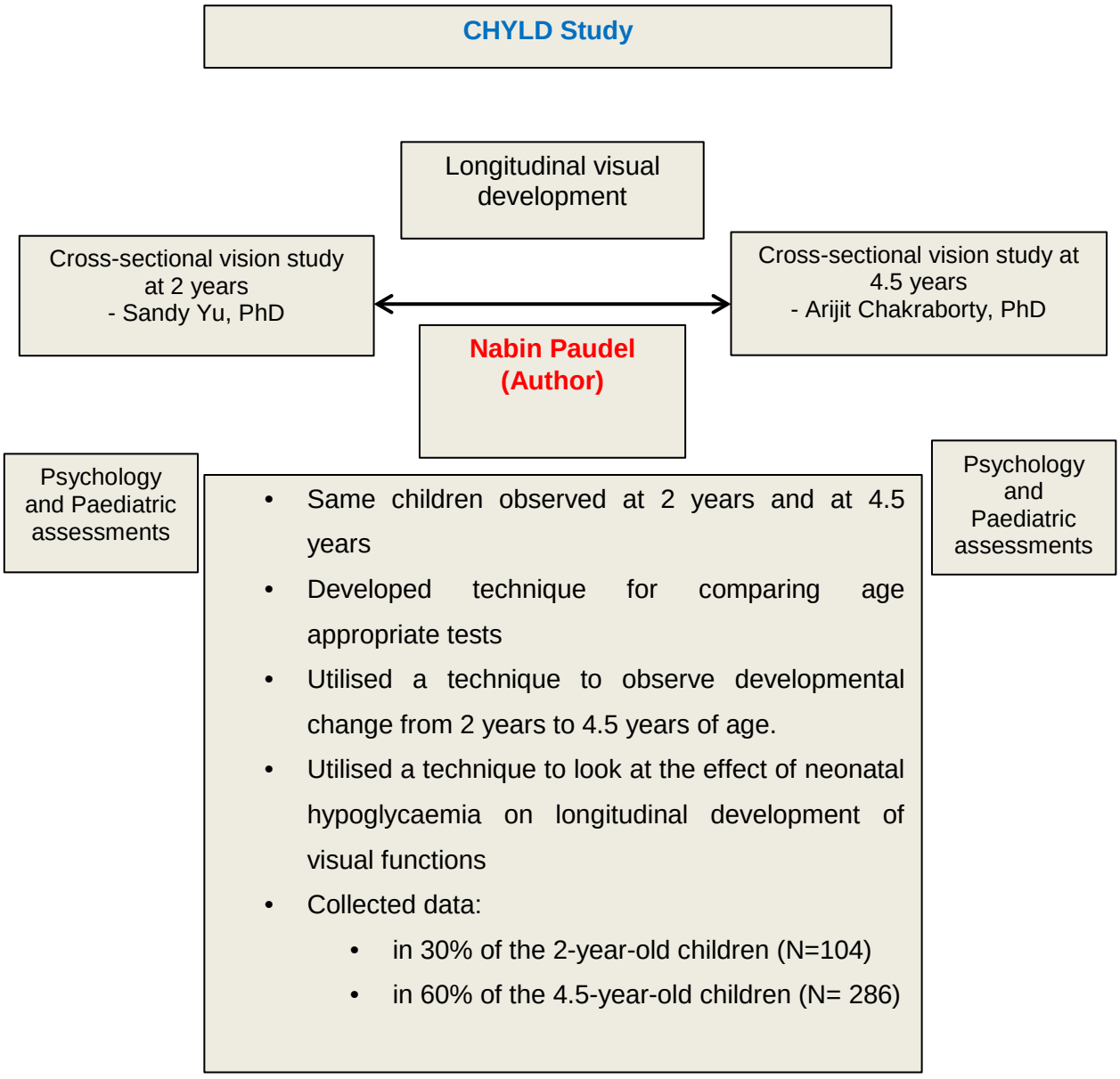

Figure 8 Overview of the CHYLD study and the role of the author in the CHYLD study

Chapter 4. Methodology

This chapter presents a detailed explanation of the vision assessment methods used for the CHYLD study and will delineate the modifications of the methods that were done to obtain adult threshold values in each of the paediatric vision tests. The adult thresholds were determined to normalise the paediatric values relative to adults. Brief outlines of the other tests that were used in the CHYLD study are also provided.

4.1. Methods used for assessing 2-year-old children

Several neurodevelopmental tests were carried out in the cohort of children at 2 years of age. These included a) a psychological assessment covering five domains: cognitive, language, motor, social-emotional and adaptive development b) a vision assessment: complete vision screening and global motion perception c) paediatric assessment: overall development and growth measures. Answers provided in a Home and Family Questionnaire was also considered. The developmental assessment was administered first and was followed by the vision and paediatric assessments. The whole session lasted approximately two hours.

Due to the lengthy nature of the session and in order to maintain the child's attention for the whole duration, clinical vision tests were chosen based on their efficiency, reliability and accuracy. Also, they were chosen based on common clinical use for this age group of children by practitioners in the Oceania and Europe. The tests were optimised for cross-sectional study considering these tests to be the most robust in detecting visual deficits in that particular age group. Dorsal visual stream function was assessed using random dot kinematogram to elicit optokinetic nystagmus. Details of the methods are provided in the following section along with some methods presented in a paper by Sandy Yu, a PhD graduate whose research was based on a sub-set of the data presented in this thesis (Yu, 2014). Her project was on the effect of NH of visual development at 2 years.

4.1.1. Vision Assessment

4.1.1.1. Visual acuity measurement

Visual acuity was assessed using the Cardiff Acuity Cards. This acuity measurement is based on vanishing optotypes and preferential looking techniques. This test has a number of rectangular neutral grey cards (a set of three for each level) with pictures of a fish, duck, car, house, train or boat on one end and blank on the other end. The pictures are computer generated and are drawn with a white band surrounded by a black band of half the width, on a neutral grey background; thus the average luminance of the target is equal to that of the grey background (Figure 8). If the target lies beyond the subject's acuity limit, it is invisible. All the pictures used are of the same overall size, but with white and black bands of decreasing width. The acuity is determined by the narrowest white band for which the target is visible. Acuity levels range from 6/60 to 6/3.8 at a viewing distance of one metre, in 0.1 log steps, which gives 12 stages of acuity levels. This test has been widely used in clinical studies and has shown a good intraobserver reliability (r=0.72 for binocular testing) and testability rate (96% in 12-month-old children, to 100% in 3-year-old children) in visual acuity measurements of children aged 1 to 3 years (Adoh & Woodhouse, 1994).

Figure 9. The Cardiff Acuity Cards. Retrieved from: http://www.kaypictures.co.uk/cardiff.html

In this study, measurement of binocular visual acuity was attempted first, followed by monocular acuity. A testing distance of one metre was maintained at all times. The testing was performed in a well-lit room whenever possible. The manufacturers' instructions were followed while testing. The threshold acuity was determined by the smallest symbol size

where the child could correctly point to an image on two out of three cards. Measurements of habitual monocular (each eye) and binocular visual acuity was attempted in all of the children. Only the measurement of the binocular visual acuity was considered for the purpose of analysis in this study. The reasons for including binocular visual acuity were as follows. Firstly, we believed that binocular acuity represents a natural form of viewing and would provide a realistic visual status of the child. Secondly, it is well understood that children have a short attention span; we often may get a single chance to assess their acuity which was mostly true in our case. We obtained binocular acuity in almost 95% of the children whereas monocular acuity was obtained in approximately 10% of the children.

4.1.1.2. Stereopsis measurement

Stereopsis was measured using the Lang I, Lang II and Frisby stereo tests. Lang and Frisby tests (Frisby, Davis, & McMorrow, 1996) were used because they have high testability in this age group (Pai et al., 2012). Lang stereo tests (Lang & Lang, 1988) use random dots together with a lenticular screen. The cylindrical arrangement of the lenticules of the screen presents a separate image to each eye. The minimum angular disparity that can be detected determines the measure of stereopsis. The Lang I stereo test consists of three images: a cat, a star and a car. They have disparity values of 1200, 600 and 550 seconds of arc respectively when used at 40 centimetres. Lang II is an upgraded version of Lang I and it provides finer measures of disparity. This test consists of three pictures: an elephant, a car and a star. These have disparity values of 600, 400 and 200 seconds of arc respectively (Figure 9). Stereopsis was determined by asking the child to point to the objects on the plate. Correct pointing to an image that has the lowest disparity value determined the threshold for that particular child.

Frisby stereo tests (Figure 11) use the principle of real depth estimation. The target and background are separated by the thickness of the plate. They are printed on opposite sides of the plates. The test consists of three plates with thicknesses of 6, 3 and 1.5 millimetres. The combination of plate thickness and testing distance allows the estimation of stereopsis, ranging from 600 seconds of arc to 5 seconds of arc. The task of the child was to identify a circle (ball) composed of geometric shapes within a mosaic of similar shapes. Each plate had four square-shaped panels containing geometric patterns and only one of the squares within the panel has the circular target. The circle was seen only by the fact that it was raised or deep compared to the background composition. The child was asked to find a hidden ball in one of the squares. The threshold was obtained when the child correctly identified the circle in the smallest disparity plate for which the circle can be identified. The Frisby test

allows for the assessment of stereo-threshold, which was important for my study; however, it is affected by head movements which induce monocular cues that may result in a better threshold for children.

Figure 10. The Lang stereo tests. Retrieved from: http://www.opticalmarketplace.co.uk/used-equipment/ophthalmic-equipment/used-accessories/omp6080/lang-stereotest-set-1-amp-2/

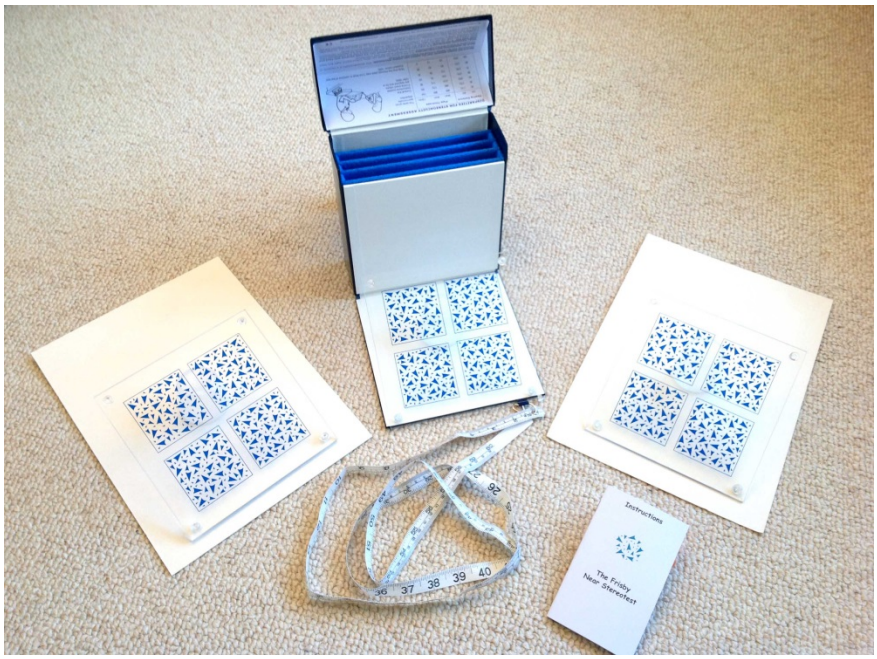

Figure 11. The Frisby stereo test. Retrieved from: http://frisbystereotest.co.uk/products/frisby-stereotest-near-assesment/

In all of the children, the Lang stereo test was attempted first followed by the Frisby test, if the children were complaint. This was because of the higher testability of Lang stereo test as compared to Frisby stereo test. Thresholds acquired with both the Lang Stereo test and Frisby stereo test were recorded in cases where both tests were performed.

4.1.1.3. Global motion perception

Thresholds for the perception of global motion were measured using random dot kinematograms (RDKs) (Newsome & Pare, 1988). The motion coherence threshold is specified as the minimum proportion of signal dots that share a common direction amongst randomly moving noise dots that allow the perception of movement in a particular direction. Following a previous study on global motion perception in infants (Banton & Bertenthal, 1996), the optokinetic reflex response was used to determine whether the direction of global motion was perceived on a particular trial.

Random Dot Kinematogram Stimuli and presentation

RDKs were generated on a MATLAB 2010a platform using the Psychtoolbox extension (Brainard, 1997) and consisted of 250 dots presented in a circular aperture of 8.3 degrees radius visual angle and bounded in a black square. The dots were white dots (luminance 138 cd/m2) on a grey background (luminance 43 cd/m^2). Each dot had a diameter of 0.5° and moved at a speed of 8° per second. Dot density was 1.16 dots/$degree^2$. The dots were presented with a varied level of coherence whereby a group of signal dots moved in the same direction (either right or left) and a group of noise dots moved in random directions. A single trial lasted for 8 seconds. Dots appeared in the screen with a limited lifetime (each dot had a 5% chance of being redrawn in a random location on any particular frame) in order to avoid tracking of a single dot which would be a measure of local motion. The stimulus was presented in a 17-inch Cathode Ray Tube monitor (Model: Dell E772p). The resolution of the monitor was 1280 x 1024 pixels. The frame refresh rate was 60 Hz.

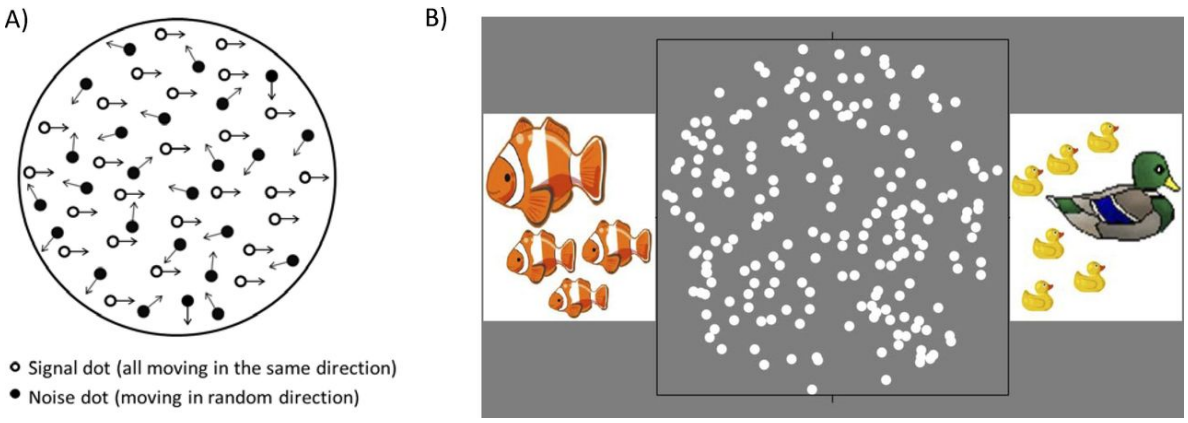

Figure 12. A) Illustration of random dot kinematogram stimulus used in our study. The filled circles represent noise dots moving in random directions. The open circles represent signal dots that are sharing a common direction (right). B) A single frame of RDK stimuli that we used for two year old children. Reprinted with permission from Investigative Ophthalmology and Vision Science, Yu et al., (2013)

The children were seated approximately 60 centimetres away from the screen. A fixation dot was present in the centre of the screen and alternated between red and green in order to get the attention of the children just before the stimuli was presented. Pictures of popular cartoon characters from well-known children's TV shows or storybooks were placed on either side of the display in order to facilitate a behavioural response (Figure 11). Based on pilot data (Yu et al., 2013), six levels of coherence were chosen to cover a broad range of possible motion coherence thresholds. These were: 100%, 84%, 68%, 52%, 36%, and 20%. The psychophysical method used to determine thresholds was the method of constant stimuli. It was not possible to use the staircase method (method of limits) in this age group because the child's responses were judging from measurement of eye movement direction and this was impossible in real time. The eye movement data were assessed offline and the minimum coherence level at which the slow pursuit and re-fixation eye movements of OKN were detected was taken as the global motion perception threshold.

Before starting the main test, the assessor made sure that the child understood the task by presenting a demonstration local motion task followed by a demonstration global motion task. The local motion task involved a single dot moving horizontally from one edge of the screen to the other. The demonstration global motion task involved presenting the stimulus (250 dots) moving in different directions with varying levels of coherence. During this demonstration an attempt was made to obtain behavioural responses (verbal or pointing responses indicating which way the child thought the dots were moving (right or left)). As

soon as the assessor felt that the children were comfortable in viewing the task, the main test was started. The levels of coherence were presented from the highest to the lowest; however, the directions of the coherently moving dots were randomly presented either right or left. In order to keep children engaged and to not lose their interest in the task, an animated video was played for ten seconds after every five stimulus presentations. Stimulus trials were presented to the children as long as they showed active interest in the test. The examiner had the option of stopping the test if he/she felt that the child was not paying enough attention to the task. A complete test involved 60 trials (10 trials for each level of coherence) and the test was designed to automatically end after 60 trials. If the children were cooperative even after 60 trials, additional trials were conducted until the child lost interest.

Determining the threshold

Just before the beginning of the test a high definition video camera (Sony HDR-CX7EK; Sony Corporation, Tokyo, Japan) was set up and was maintained in auto focus mode. The camera was placed towards the right side of the display monitor, angled so that there was a clear view of the child's eyes when they looked at the monitor. The whole session of the motion coherence task was recorded on video. The video clip was later analysed offline, manually, by a single assessor. The assessor was masked to stimulus direction while analysing the video footage. The assessor carefully evaluated each of the children's sessions against various factors. The assessor judged the validity of the eye movements based on the quality of recordings, eye position in the video frame and the child's fixation behaviour. A minimum of 3 trials for at least 5 coherence levels (minimum of 15 in total) was required to be included for threshold analysis. The presence or absence of OKN eye movements in response to the stimuli direction was the main criteria for grading.

After the judged eye movement direction had been compared with the direction of the stimulus presented, the proportion correct for each difficulty level was collated. The frequency of seeing curve was fitted using Weibull function in Palamedes toolbox in MATLAB for analysis (Prins & Kingdom, 2009). The Weibull function provides an estimate of threshold to a level where the participant has correctly responded to the stimuli 63.2% of times. Mathematically, the Weibull function can be denoted as:

$$F_W(x = \alpha; \alpha, \beta) = 1 - e^{-(x/a)\,\beta}$$

Where F_W = Weibull function, x = the coherence level, β = rate of change (slope) and α = the threshold. The MATLAB code to provide an appropriate psychometric fit was implemented with 4 parameters as input variables which were - estimate of threshold, estimate of slope, guess parameter and lapse parameter. The output generated 6 variables which included calculated threshold from the input data, calculated slope, standard error of the threshold, standard error of the slope and two values for goodness of fit. A maximum likelihood criterion was applied in order to obtain the threshold. The psychometric fit was considered an acceptable fit is the p value for the goodness of fit was >0.05.

Test-retest reliability of this psychophysical method was assessed by performing the test in a group of fifteen normal children aged between 21 to 27 months on two separate occasions using the same protocol as that of the CHYLD study children. The average difference in the threshold between these two occasions was 0.94% (95% CI- 3.45-1.54, p=0.44). The 95% limits of agreement between the two occasions were ±9.00% (Yu et al, 2013).

To determine the validity of the test (i.e. how well the thresholds determined by eye movement analysis correlated with the thresholds obtained via behavioural method) motion coherence thresholds were assessed in normal adults using both methods. The experiments proved that the test was valid and the estimates of threshold obtained via eye movements were well correlated with the behavioural measures. (Intra-class correlation = 0.81, 95% CI= 0.41-0.95, p=0.001) The limits if agreement between the two measures were ±2.5%.The details of these experiments, which were led by another investigator, are explained elsewhere (Yu et al., 2013).

4.1.1.4. Refractive error and general ocular health

Non-cycloplegic refraction was attempted either with a Welch Allyn Suresight handheld autorefractor or by manual retinoscopy. An evaluation of external ocular health was performed by inspecting external ocular features for any abnormalities. Internal eye health screening was conducted by observing the direct and consensual pupillary light reflex and red fundus reflex with the use of an ophthalmoscope. Eye alignment was assessed using a unilateral cover test and the Hirschberg corneal reflex test. A twenty-prism dioptre test was applied in order to assess binocular fusion. Ocular motility testing was carried out by asking the child to keep his/her head still and follow an interesting toy or a flashing object in all of the cardinal positions of gaze. Any abnormalities found during these tests were noted.

4.1.1.5. Referral

The referral criteria for visual abnormalities were determined after a careful discussion by a panel of ophthalmologists and optometrists and were based on preschool screening guidelines from the National Eye Institute Task Force on Vision Screening in the Preschool Child (Hartmann et al., 2001) and clinical experience. They were as follows:

Reliable retinoscopy or autorefractor findings of:

≥ 1.00 D for anisometropia in any meridian

≥ 1.50 DC of astigmatism

< -2.00 D of myopia and

≥ +3.50 D of hyperopia

Any obvious abnormalities of external ocular structures

Any abnormal findings in red reflex or pupillary reaction

Any obvious ocular alignment issues

Inability to perform binocular or monocular Cardiff Acuity Test

Habitual binocular visual acuity of worse than 0.5 logMAR

4.1.2. Developmental Assessment

The children were assessed for their neurodevelopment under two different categories using different tools. The tools were: Bayley's Scales of Infant development – Third Edition (BSID-III), developmentally sensitive executive function tests along with the Behavior Rating Inventory of Executive Function®–Preschool Version (BRIEF®-P) questionnaire (distributed by PAR, Florida, US). The assessments were administered either by a psychologist or by an accredited research nurse.

4.1.2.1. Bayley Scales of Infant Development – Third Edition (BSID-III)

The BSID-III is a standardised instrument consisting of a sequence of test items administered to assess development of children between 1 and 42 months of age. The instrument assesses child development in five broad domains: cognitive (focuses on mental development with some use of language domain), language (receptive and expressive communication skills), motor (fine and gross motor skills focusing on the quality of a child's movement), social-emotional scale (assesses social and emotional development milestones based on a questionnaire completed by the child's caregiver), and, adaptive (assesses the independency of the child in daily living skills) (Pinon, 2010).

4.1.2.2. Executive function tests

Executive function tests assess high order cognitive processes for monitoring and control of thought and action, which are thought to be the function of the frontal lobe of the brain. Age appropriate tasks were chosen for this cohort based on a study by Carlson (Carlson, 2005) in combination with the standardized questionnaire-based tool: Behavior Rating Inventory of Executive Function®–Preschool Version (BRIEF®-P) (Sherman & Brooks, 2010). The BRIEF®-P is completed by the parent or caregiver or the child's teacher. It measures the following domains of executive function: inhibit, shift, emotional control, working memory and plan/organize. The parent or caregiver completed the questionnaire on the date of the assessment.

4.1.2.3. Paediatric assessment

Assessment of the physical and medical status of the child was performed in this session. This included measures of height and growth, along with a brief medical history of the child being taken in consultation with the parents. The assessment was carried out either by a paediatrician or by an accredited PhD student in paediatrics.

4.1.2.4. Home and Family Questionnaire

A set of questionnaires was sent to the family in advance of the date of the assessment. The questionnaires included demographic characteristics and socioeconomic status of the family and covered items such as gender, date of birth, income, family size, education, maternal health during pregnancy and breastfeeding.

4.2. Methods used for assessing 4.5-year-old children

The assessment at 4.5 years also involved a range of neurodevelopmental tests. These tests included: a) a psychological assessment looking for five domains: cognitive, language, motor, social-emotional and adaptive, b) executive function assessment, c) visual function assessment: complete vision screening and global motion perception, d) paediatric assessment; overall development and growth measures, and, e) answers provided in a Home and Family Questionnaire were also considered.

The developmental assessment was administered first, followed by the vision and paediatric assessments. The whole session lasted for approximately two and half hours.

Age appropriate visual function tests were chosen to assess visual function in this group. As the cognitive ability of children in this age group permits the assessment of visual function using tests that provide findings close to that of gold standard adult vision tests, such tests were chosen. Details of the methods are provided in the following sections.

4.2.1. Vision assessment

4.2.1.1. Visual acuity measurement

The Lea Symbols test (Hyvarinen et al., 1980) was used to assess visual acuity in the 4.5-year-old children. This test was specifically chosen because previous studies have confirmed that acuity findings obtained with this test are comparable to the gold standard visual acuity test (Early Treatment Diabetic Retinopathy Study chart or Bailey Lovie logMAR chart) (Dobson, Clifford-Donaldson, et al., 2009). Furthermore, the Lea Symbols test has a testability rate of 80% to 90%, which is one of the highest rates achievable in assessing

children aged 3-5 years (Becker et al., 2002). The test consists of four shapes: apple, house, circle and square. The shapes are designed in such a way that when all of the shapes are equally blurred they appear as a diffuse ring with a light cross at the centre when the threshold size is reached. For this study, a flip card version of Lea Symbols was used (Figure 12), where in each card the five optotypes have a horizontal arrangement surrounded by a black rectangle in order to enhance crowding. The test was performed at three metres distance where the measurable levels of visual acuity ranged from 0.6 logMAR to -0.2 logMAR. Optotype by optotype scoring (Bailey, 2006) was applied in the test results. The child was comfortably seated, three metres away from the test card, and asked to either name or match the same shape on his/her key card as pointed to by the assessor. The test was continued until the child could not read or match any optotypes on a particular line.

Figure 13. The Lea Symbols Test.

Retrieved from: https://www.good-lite.com/Details.cfm?ProdID=206&category=1&Secondary=73

Presenting binocular visual acuity testing was followed by monocular testing in all of the children. Only the measures of binocular visual acuity were considered for data analysis as we were able to assess only binocular acuities in most of the 2 year old children.

4.2.1.2. Stereopsis measurement

The Vision Assessment Corporation Fly Stereo Acuity Test with Lea Symbols® P/N 1000 (Figure 13) was used to assess stereopsis at 4.5 years. This test is based on the Polaroid® vectographic principle. It consists of two target objects imprinted within a polarising medium

such that each target is polarized 90 degrees with respect to one another. When viewed through using glasses containing appropriately oriented polarising analysers, each of these images is seen separately by each eye. The angular disparity between these components of the two imprints enables the measurement of stereopsis. This test can measure stereopsis ranging from 4800 seconds of arc to 20 seconds of arc. It has three panels of targets. The left-hand side panel of the test booklet has an imprint of a housefly. The body parts of the housefly are divided into four components depending upon their disparity values. The top half of the right-hand side panel of the booklet consists of ten boxes, each with four circles. Only one of the circles in each of the boxes appears to be floating above (or below; depending on the orientation of the analysers) the others. The lower half of the right -hand side panel consists of three lines, having four Lea symbols in each line. Only one of the symbols appears to be floating above others. The stereopsis values of each of the test panels are presented in Table 5.

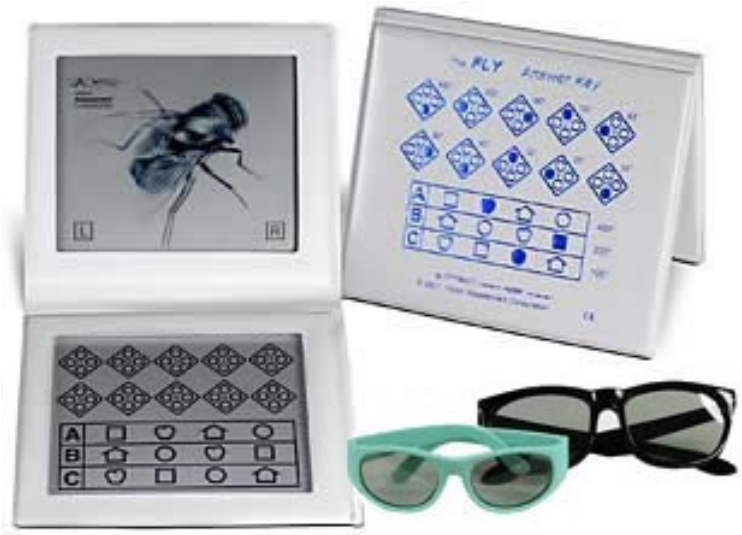

Figure 14. The Vision Assessment Corporation Fly Stereo Acuity Test with Lea Symbols Picture retrieved from https://www.goodlite.com/cw3/Assets/documents/100050_StereoFlyManual.pdf

Table 5 Targets and their corresponding stereopsis values in the Fly stereo test

Target	Stereopsis (seconds of arc)
Housefly	
Right Wing Left Wing Thorax Eyes	4800 3500 3200 3000
Circles (10 boxes)	400, 200, 160, 100, 63, 50, 40, 32, 25 and 20 (from the top left box to the bottom right box)
Lea Symbols	400, 200 and 100 (from top line to bottom)

For testing, the children were first comfortably seated on a chair or on their parent's lap. The assessor then presented the booklet and asked the child to pinch the wings of the fly to show that the child understood the task. Once the assessor was sure that the child understood the task, the assessor moved on to the boxes with circles. Starting from the first box, the child was asked to point to one of the circles that appeared to be floating or was different from the others. The testing was stopped when one box was missed. The preceding box was retested to make sure that the stereo threshold was an accurate estimate and not based on the child having guessed. If the child missed the preceding box, the test was started two to three box before the preceding box and the lowest disparate box where a correct response was given was noted.

4.2.1.3. Measurement of Global motion perception

RDK stimuli were used to assess global motion perception. The parameters of the stimuli were carefully chosen, as recommended by previous studies, to specifically target dorsal stream defects in children born at risk of abnormal neurodevelopment, and were closely matched to studies of global motion perception in children by Narasimhan & Giaschi (2012), Gunn et al. (2002) and Lewis & Maurer (2005). In contrast to the methods used at 2 years, the method used at 4.5 years was different. Instead of optimizing the stimuli for OKN, the method was designed to facilitate behavioural testing. This was done because the children did not cooperate with the stimulus that was used for 2 year-olds. This was primarily because the stimulus was unable to sustain attention of these children. Furthermore, this

method has been widely used in previous studies (Lewis & Maurer, 2005; Narasimhan & Giaschi, 2012) and is currently considered as the gold standard method for determining global motion perception.

Random dot kinematogram stimuli and presentation

RDK stimuli (Figure 12) were designed on a MATLAB 2010a platform with the use of psych toolbox extension. The test stimuli consisted of 100 dots, presented in a circular aperture of 10 degrees diameter visual angle, bounded by a black square. The dots were white (luminance 137 cd/m^2) on a grey background (luminance 45 cd/m^2) (Figure 14). Each dot had a diameter of 0.24 degrees moving at a speed of 6° per second. The dots moved 0.17 degree per 17 milliseconds in order to achieve the desired speed. Dot density was 1.27 dots/$degree^2$. The dots were presented with a varied level of coherence, with a group of signal dots that move in the same direction (up or down) and a group of noise dots that move in a random direction. A single trial lasted for one second. Dots appeared in the screen for a limited lifetime (each dot had a 5% chance of being redrawn in a random location on any particular frame) in order to avoid tracking of a single dot, which would be a measure of local motion. The lifetime of the dots was 300ms. The stimulus was presented in a 17-inch Cathode Ray Tube monitor (model: E771p). The resolution of the monitor was set at 1024 x 768 pixels. The frame refresh rate of the monitor was 120 Hz. The testing distance was maintained at 60 centimetres.

The test parameters were designed and optimised in collaboration with another PhD colleague Arijit Chakraborty. The use of this method in order to assesses global motion perception has been reported previously by Chakraborty et al., (2015).

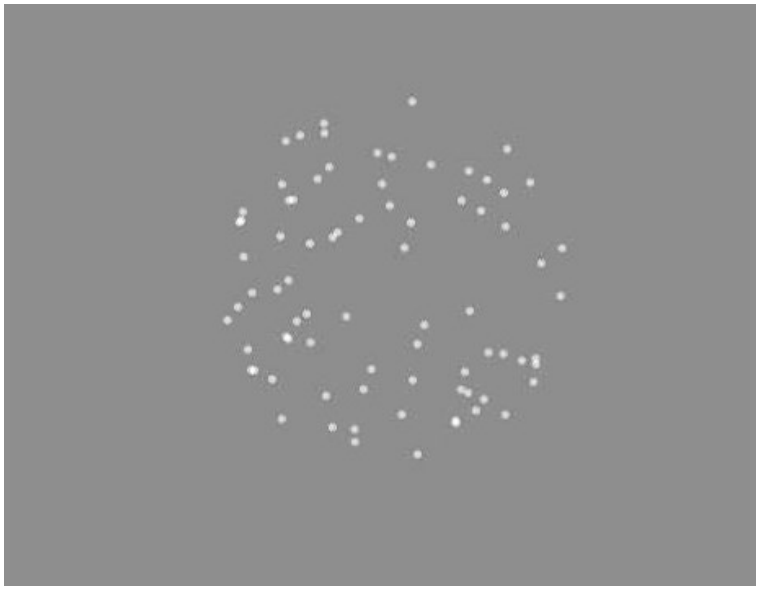

Figure 15. A single frame of random dot kinematogram stimuli used for 4.5-year old children

Before starting the real test to determine the actual threshold, the assessor made sure that the children understood the task by familiarizing them with a demo global motion task. For the demo task, the assessor started with a stimulus at 100% coherence. After four successive correct responses on that level the assessor varied the coherence and familiarized the participant with lower levels of coherence. The actual test to determine threshold was started once the assessor determined that the children understood the task.

Determining the threshold

The stimuli were presented in a 2 down 1 up staircase fashion. This method converges on the 71% correct response. (Levitt, 1971) The test started with a 100% coherence level and varied accordingly depending upon the response of the child. The proportional step size was maintained as 50% for the first reversal and 25% thereafter. The test was designed to automatically end after five reversals and the threshold was calculated by taking the mean of the last four reversals.

4.2.1.4. Refractive error and general ocular health

Non-cycloplegic refraction was attempted using a manual retinoscopy. External ocular health was performed by inspecting external ocular features for any abnormalities. Internal eye health screening was conducted by observing the direct and consensual pupillary light reflex and red fundus reflex with the use of an ophthalmoscope. Eye alignment was assessed using a unilateral cover test and the Hirschberg corneal reflex test. A twenty-prism dioptre test was applied to assess binocular fusion. Ocular motility testing was carried out by asking the child to keep his/her head still and follow an interesting toy or a flashing object in all of the cardinal positions of gaze. Any obvious abnormalities found during these tests were noted.

4.2.1.5. Referral

The referral criteria for visual abnormalities were determined by a panel of ophthalmologists and optometrists and were based on preschool screening guidelines from the National Eye Institute Task Force on Vision Screening in the Preschool Child (Hartmann et al., 2001) and clinical experience. They were as follows:

Reliable retinoscopy finding of:

≥ 1.00 D for anisometropia in any meridian

≥ 1.50 DC of astigmatism

< -2.00 D of myopia and

≥ +3.50 D of hyperopia

Any obvious abnormalities of external ocular structures

Any abnormal findings in red reflex or pupillary light reaction

Any obvious ocular alignment issues

Inability to perform binocular or monocular Lea Symbols test

Presenting binocular or monocular visual acuity of worse than 0.3 logMAR

Difference of presenting acuity of more than 0.1 logMAR between each eye

4.2.2. Developmental Assessment

The children were assessed for their neurodevelopment under four different categories using different tools. The tools were: Wechsler Preschool and Primary Scale of Intelligence – Third Edition (WPPSI-III) (Preschool, 2002), Beery-Buktenica Developmental Test of Visual-motor Integration (VMI), 6th Edition (Beery, 2004), Executive function tests (Carlson, 2005), along with Behavior Rating Inventory of Executive Function®–Preschool Version (BRIEF®-P) questionnaire (distributed by PAR, Florida, US) (Guy, Isquith, & Gioia, 2004), and Movement Assessment Battery for Children (ABC) (Sudgen, Henderson, & Barnett, 2007). The tests were administered either by a registered psychologist or by an accredited research nurse.

4.2.2.1. Wechsler Preschool and Primary Scale of Intelligence – Third Edition (WPPSI-III)

The WPPSI-III measures intellectual functioning of children in two cognitive fields: verbal IQ and performance IQ. Verbal IQ involves hearing a task and responding verbally, whereas performance IQ involves visual input and vocal and motor output. Standard scores of the test have a total score of 100, with a standard deviation of 15. The subtests have a scaled total score of 10, with a standard deviation of 3. This test assesses the following aspects: information, vocabulary, word reasoning, comprehension, similarities, receptive vocabulary, picture naming and block design.

4.2.2.2. Beery-Buktenica Developmental Test of Visual-motor Integration (VMI), 6th Edition

The Beery-Buktenica Developmental Test of Visual-motor Integration assesses one's ability to integrate visual and motor skills. It also measures visuoperceptual and coordination ability. The task involves a pencil and a paper and the child is asked to copy different shapes in increasingly complex fashion.

4.2.2.3. Executive function tests

Age appropriate executive function tests were administered along with the Behavior Rating Inventory of Executive Function®–Preschool Version (BRIEF®-P). Some of the tasks performed by the children included gift wrap delay (simple response inhibition), bear/dragon (complex response inhibition) and the day-night Stroop task (complex response inhibition). In addition, the BRIEF®-P was completed by the parent or caregiver on the same day as the assessment.

4.2.2.4. Movement Assessment Battery for Children (ABC-2)

The Movement ABC is designed to detect children with movement difficulties. It includes series of tasks that assess motor skills in children. Children are assessed in a strictly specific way over three broad tasks: manual dexterity, aiming and catching, and balance.

4.2.2.5. Home and Family Questionnaire

A set of questionnaires was sent to the family in advance of the date of the assessment. The questionnaire included information on demographic characteristics and socioeconomic status of the family and included items such as gender, date of birth, family income, family size, education, maternal health during pregnancy and breastfeeding.

4.3. Vision assessment in adults

4.3.1. Visual acuity measurement in adults

Visual acuity assessment in adults was conducted in exactly the same way that was done for 2 year-old children and 4.5 year-old children except for the Cardiff acuity cards test where the distance was increased to 3 meters (rather than a distance of 50 cm or 1m). This was done to provide stimuli that were small enough for the adult threshold values.

4.3.2. Stereopsis measurement in adults

The measurement of stereopsis test that was used for 4.5 year old children was done in adults in the exact way as it was for children. However, for the test that was used for 2 year old children - the Frisby stereo test, the distance was increased until the threshold was obtained. The Lang stereo test (another test that was used at 2 years) was conducted exactly in the same way that was done for the CHYLD study participants.

4.3.3. Global motion perception measurement

To determine adult threshold, the test used for 4.5 year old children was performed exactly in the same way that was done for the CHYLD study children. For the RDK stimuli used for the two year old children, instead of presenting the coherence levels at 100%, 84%, 68%, 52%, 36%, and 20% the following coherence levels were presented - 20%, 12%, 8%, 6%, 4% and 2% so that thresholds could be reached.

4.4. Vision Assessor:

Visual assessment for both the 2-year-old cohort and 4.5-year-old cohort was carried out either by a New Zealand registered optometrists who had experience in assessing children or by an optometrically trained accredited PhD students.

4.5. Data used in this thesis

To address the aims and objectives outlined in sections 1.2.1 and 1.2.2 the following datasets from the CHYLD study cohort were used in this thesis:

2-year assessment

Visual acuity

Stereopsis

Global motion perception

General ocular health

4.5-year assessment

Visual acuity

Stereopsis

Global motion perception

General ocular health

4.6. Data analysis

Data analysis and data visualisation was conducted using SPSS v.21 and Microsoft Excel, 2013. The distribution of data was checked for normalcy for each of the variables using Kolmogorov-Smirnov Goodness-of-fit test. It was observed that most of the variables in our study were not normally distributed; hence non-parametric tests were implemented for most of the analysis. Most of the data is presented as median and interquartile range. Mann

Whitney U test was used for independent samples. Wilcoxon-signed Ranks test was used for paired samples. Spearman correlation was used to determine the relationship between function at two different ages. Where the non-parametric equivalents to the parametric tests were not available, parametric tests were applied. Parametric tests were still applied where the distribution was close to normalcy and the skewness and kurtosis values permitted their use. Graphs and figures were plotted either using SPSS or Microsoft Excel or Sigma Plot statistical software.

4.7. Data normalisation

Visual function data from children were normalised to the median adult threshold values obtained using the same tests. As will be mentioned in section 5.6 the decision to normalise the data was based on our preliminary analysis on the development of visual acuity from 2 years to 4.5 years which was in contrast to our expectation. We observed reduction in median visual acuity from 2 years to 4.5 years. We found that the most likely cause of the finding was due to the employment of age appropriate tests. Hence the normalisation was done to allow comparisons to be made between the different tests used at different ages. Previous studies have used a similar approach to track visual development (Carkeet et al., 1997; Teller, 1997). For this purpose, 15 adults from age 22 to 35 years were recruited. Each of the adults performed all of the visual function tests that were administered in these children at age 2 years and age 4.5 years.

Even though the normalisation method transforms values obtained with different methods to a common metric (ratio) and make it easier for comparison, it must be acknowledged that this method is not without limitations. After normalisation, there is a loss of raw information and may increase variability of the data that may lead to uncertainty in the confidence intervals.

As mentioned earlier, the primary aim of transforming the children's data into ratios in this study was to generate a common metric so that the measures obtained with different tests are comparable. However, this process of data transformation can also be used to normalise the skewed distribution of the data so that more robust parametric tests could be implemented. (Dallal, 1999) We tried to normalise our data distribution using various data transformation methods such as ratio, log of ratios, square root, multiple of medians, and logs but none of these data transformations converted our data into a symmetric or normal

distribution. Moreover, the results obtained using log transformed values and ratios were not considerable different and hence we employed our analysis using ratios.

4.7.1. Normalisation of the binocular visual acuity data:

Binocular visual acuity was normalised by determining the difference between the individual data of the children and the median adult threshold acuity obtained using the same tests. See example below for clarification:

Example for 2 year-old data:

Raw binocular VA of a child with Cardiff acuity test at 2 years= 0.00 logMAR

Adult median binocular acuity threshold using Cardiff Acuity test = -0.46 logMAR

Normalised Binocular Acuity at 2 years = Raw binocular VA of children at 2 years – adult median threshold with Cardiff acuity test.

= 0.00- (-0.46) = 0.46 logMAR

Example for the 4.5 year-old data:

Raw binocular VA of a child with Lea Symbols at 4.5 years= 0.1 logMAR

Adult median binocular acuity threshold = -0.14 logMAR

Normalised Binocular Acuity value at 4.5 years = Raw binocular VA of children at 4.5 years - adult median threshold with Lea Symbols

= 0.10- (-0.14) = 0.24 logMAR

The change in normalised VA was calculated by subtracting normalised BVA at 4.5 years from normalised BVA at 2 years.

= 0.46-0.24= 0.22 logMAR change from 2 to 4.5 years

The 4.5 year VA measurement was subtracted from the 2 year VA measurement. Therefore positive values indicate an improvement in VA from 2 to 4.5 years.

4.7.2. Normalisation of the stereoacuity and the global motion perception data:

Normalisation for stereopsis and global motion perception data were determined by division. See below for examples:

Raw Frisby stereopsis of a child at 2 years = 340” of arc

Adult median stereoacuity threshold using Frisby= 22” of arc

Normalised Frisby stereoacuity of the child at 2 years = 340/22 = 15.45

Change in visual function was determining by calculating the difference between the measures at age 2 and 4.5 years.

Change in stereopsis / global motion perception from 2 to 4.5 years = Normalised values at 2 years – Normalised values at 4.5 years.

Even though the logMAR values of visual acuity were normalised using subtraction, they are essentially equivalent to the ratio of MAR values. Therefore the values were normalised consistently for all three domains of visual function.

Chapter 5. Comparison of visual acuities measured using the Cardiff Acuity Cards, the Lea Symbols and the ETDRS chart in adults with normal vision

This experimental chapter investigates the relationship between the Cardiff Acuity Cards (the acuity test used at 2-years of age) and the Lea Symbols test (the acuity test used at 4.5-years of age) and compares the findings from both tests with the gold standard ETDRS chart. Normal adult observers were used in this study.

5.1. Introduction

The aim of this study was to compare visual acuity measurements made using the Cardiff Acuity Cards (CAC) and the Lea Symbols (LS) to assess whether these two tests provide comparable estimates of visual acuity. This question is important because the Cardiff Acuity Cards were used within the 2 year CHYLD study assessment and the Lea Symbols were used within the 4.5 year CHYLD study assessment.

This study was motivated by a preliminary analysis of binocular visual acuity development from 2 years to 4.5 years of the children enrolled in the CHYLD study cohort. The result demonstrated that the median binocular visual acuity of the 4.5-year-old children was worse than the median binocular visual acuity of the 2-year-old children. It is well known that visual functions improve as visual maturation occurs with age and therefore this result was unexpected. We hypothesised that this effect was due to the use of different age appropriate tests at each age. However, there was no evidence in the literature on the relationship between visual acuity measurements made using the CAC vs. the LS. Hence, this study was designed to explore whether the CAC and the LS provide comparable measures of visual acuity and to validate if the raw measures obtained with these tests are appropriate to be used for an assessment of the longitudinal development of visual acuity. Adult participants were used for this validation study to ensure that there was no effect of cognitive function on test performance (i.e., both tests could be easily understood and performed by adults). In addition, measures were made using the Early Treatment of Diabetic Retinopathy Study (ETDRS) chart to provide a gold standard reference. Measurements were made both under best corrected conditions and with the introduction of (1) spherical defocus using plus spherical lenses, and (2) astigmatic defocus using Jackson crossed cylinder (JCC) lenses to simulate the presence of refractive errors and to obtain a range of visual acuities that would simulate reduced vision as might be expected in some cases of NH. It has been shown in

previous studies that defocus interacts differently with different paediatric acuity charts (Formankiewicz & Waugh, 2013; Little, Molloy, & Saunders, 2012) and hence we were also interested in how defocus interacted with the paediatric acuity charts that we used for the CHYLD study. This aspect of the study addressed the question of whether the Cardiff Acuity Cards and Lea Symbols provide similar visual acuity estimates under different levels of reduced vision due to refractive errors.

5.2. Materials and methods

5.2.1. Visual acuity charts

Three acuity charts, two commonly used paediatric acuity charts (Cardiff Acuity Cards and Lea Symbols), and one adult acuity chart (ETDRS) were used. Both of the paediatric charts were used within the CHYLD study assessments as described in Chapter 4. The stimuli in the CAC test are designed using the vanishing optotype principle. This test is commonly used for assessing vision in toddlers because the stimuli are presented using a two-alternative, forced choice protocol, and the child's responses can be observed from their preferential gaze directions during the test. The Lea Symbols (LS) chart is among the most widely used recognition-based test for children 3 years of age and over, and it fulfils all of the international visual acuity chart guidelines (Anstice & Thompson, 2014). The ETDRS chart is considered as the gold standard chart for use with adults and was used to compare findings obtained from these two paediatric tests. The comparison allowed us to assess whether either test over or underestimated visual acuity.

5.2.2. Participants

Adult observers were chosen for the study because their performance would not be altered by the differing cognitive demands of each test. Subjects were eligible to participate if they were at least 16 years of age, had best corrected visual acuity of at least 0.1 logMAR, measured on a standard Bailey-Lovie chart, and no self-reported ocular pathology. Forty-three participants were recruited. All of the participants first underwent testing in the focused condition with each of the tests. They were then split into two groups according to the order in which they were recruited. One group (N=23) participated in the spherical blur experiments, while the second (N=20) underwent the astigmatic blur testing phase of the study. This approach was adopted to manage the time required to complete each of the

different combinations of chart and blur level. Prior to all experiments, all participants underwent a standard refractive examination, and the resulting spectacle prescription was placed in a standard trial frame for all acuity measurements. The vertex distance was kept to a minimum.

5.2.3. Acuity measurements

The procedures used in administering the CAC acuity and LS acuity tests were exactly the same as those used for the CHYLD study participants except for the CAC, where the test distance was increased from one metre to three metres to ensure that threshold measures could be obtained. The acuity results were calculated taking the longer testing distance into account. As preferentially directed eye movements were difficult to judge from this increased testing distance, participants were asked to verbally indicate whether the vanishing optotype was located on the upper or lower half of the card. A requirement to indicate picture location rather than naming of the picture was chosen because this type of response is closest to that which children provide for this test, where they look at the picture but are not asked to name it. The Lea Symbols chart was viewed at a distance of three metres and the same optotype-by-optotype scoring method used in the CHYLD study was implemented to determine the threshold acuity. The testing was conducted in a well-illuminated examination room (luminance). All measures were monocular, with the left eye occluded. Monocular measures were used to facilitate the introduction of defocus.

5.2.3. Spherical defocus

Subjects were six males and seventeen females, aged 17 to 34 years (mean: 24 years ±3.66 SD). After completing measures on each acuity chart under focused conditions, spherical lenses of the powers +1.00D, +2.00D, +3.00D were introduced. In order to minimize learning and fatigue effects, the order of testing was randomized across all possible combinations of blur level and chart type. The dioptric powers were chosen from +1.00 to +3.00 D in 1 dioptre steps because most of the preschool children have refractive errors within this range.(Dirani et al., 2010; Giordano et al., 2009)

5.2.4. Astigmatic defocus

Subjects were six males and fourteen females, from 22 to 30 years of age (mean: 24.25 years ±2.5 SD). Astigmatic refractive error was simulated using Jackson crossed cylinder (JCC) lenses of powers ±0.50 DC, ±1.00 DC and ±1.50 DC. The range of dioptric power was chosen based on the range of astigmatism that is common in preschool children.(Cowen & Bobier, 2003; Harvey, 2006) JCC lenses were employed as they have the benefit of separating the focal lines by a known amount, whilst maintaining the circle of least confusion (COLC) on the retina. Furthermore, the issue of optotype magnification in a certain direction while using the plano-cylindrical lenses is avoided by the use of JCC. The orientations of the minus axis of the JCC lens used for each JCC power in the simulation of astigmatic refractive error were 45°, 90° and 180°. Only 45 degree axis orientation was implemented for simulating oblique astigmatism. This was done knowing that addition of more trails would be time consuming and the assumption that participant fatigue would lead to more variability within the data. The sequence of chart type, defocus level and astigmatic defocus axis orientation was randomized across participants.

5.3. Data Analysis

The notation for astigmatic defocus is presented in the form of power vectors (Thibos, Wheeler, & Horner, 1997) with M for sphere, J_0 for crossed cylinder axes at 90 and 180 degrees, and J_{45} for oblique astigmatism (45 and 135 degrees). Negative values for J_0 represented the astigmatic defocus for the negative cylinder at 90 degrees orientation. The data was analysed using SPSS Version 21 and visual presentation of data was carried out using Microsoft Excel 2010 and SPSS. Non-parametric statistical tests were employed because the data sets were not normally distributed. Mean and median values did not differ from one another for these data and, therefore, means (+/- SD) are shown as summary statistics to facilitate comparison with previous work.

5.4. Results

5.4.1 Relationship between tests

In the focused condition, there was a moderate and statistically significant correlation between CAC and LS (rho=0.40, p=0.007) (Figure 15), suggesting that these two tests provide partially related measures of visual acuity. There was also a significant correlation between LS and ETDRS acuity (rho=0.48, p=0.001) but there was no significant correlation between CAC and ETDRS acuity (rho=0.24, p=0.12).

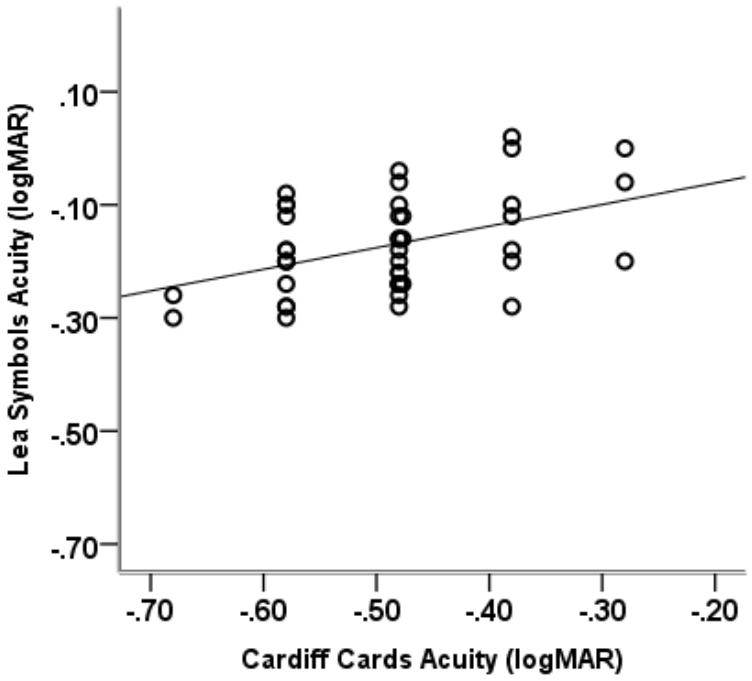

Figure 16. Relationship between the Cardiff Acuity Cards and Lea Symbols acuity under focused conditions in adults (N=43). The solid line represents a trend line.

5.4.2. Agreement between tests

A Bland-Altman chart (Figure 5.2) was plotted to quantify the difference between the CAC and LS tests. In the focused state, Cardiff Acuity Cards overestimated acuity by approximately 0.3 logMAR (3 lines) in comparison to both the Lea Symbols and ETDRS charts. The mean difference between Cardiff Acuity Card results and measurements from the ETDRS chart was -0.31±0.10 logMAR. The Mann-Whitney U test revealed that the

scores obtained with CAC and ETDRS were statistically significantly different (Z= -7.91, p<0.001). The mean difference between CAC and LS was -0.31±0.09 logMAR, which was also statistically different (Z= -7.94, *p*<0.001). However, no difference was observed between acuities measured using the LS and the ETDRS charts (mean difference 0.00±0.08 logMAR, Z= -0.16, *p*=0.86).

The 95% limits of agreement between the CAC and the LS tests were ±0.20 logMAR (Figure 16) which was similar to the 95% limits of agreement between the LS and the ETDRS charts (±0.15 logMAR), and CAC and ETDRS (±0.20 logMAR).

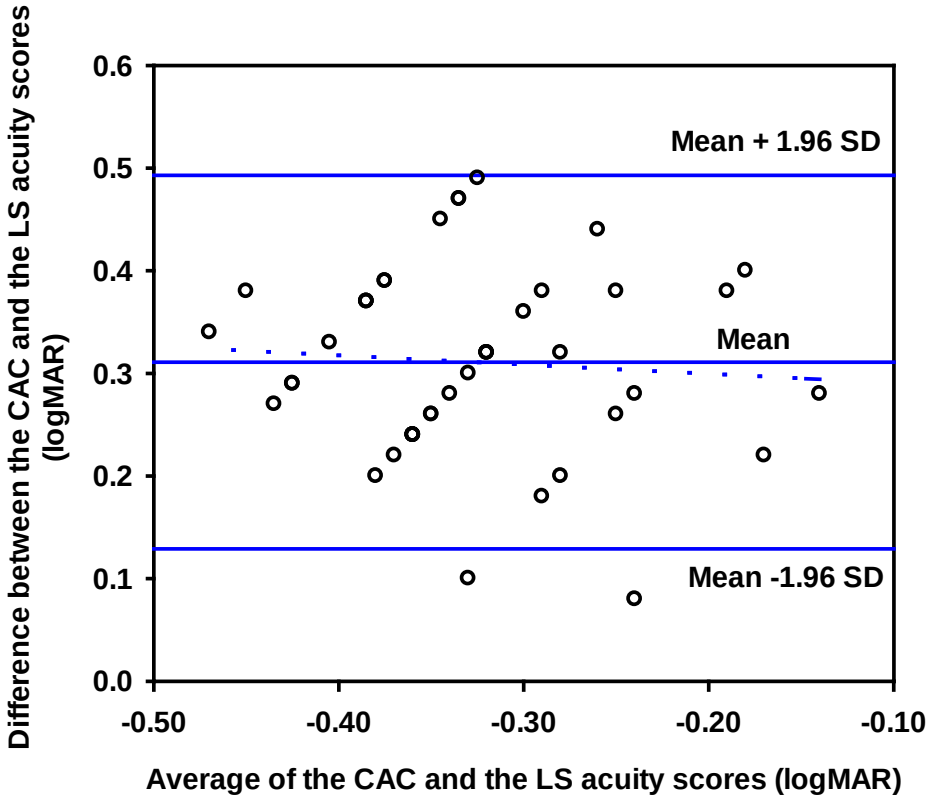

Figure 17. Bland-Altman chart demonstrating the agreement between acuities measured using Lea Symbols and acuities measured with Cardiff Acuity Cards (the dotted blue line represents the regression line)

The acuity scores obtained with the Lea Symbols test and the ETDRS test were in close agreement with one another. The 95% confidence interval of the mean differences was from -0.15 to +0.15 logMAR. The range was 0.3 log minutes of arc, which was equivalent to three lines on a logMAR chart.

When the measures of focussed and defocussed conditions were combined and compared between the CAC test and the LS test, a considerably higher bias was observed. Mean bias was 0.46 logMAR, which was approximately 4 and half lines on a standard logMAR chart.

The 95% confidence interval of the mean difference was 0.08 to 0.84 logMAR. The limits of agreement were ± 0.44 logMAR. (Figure 18)

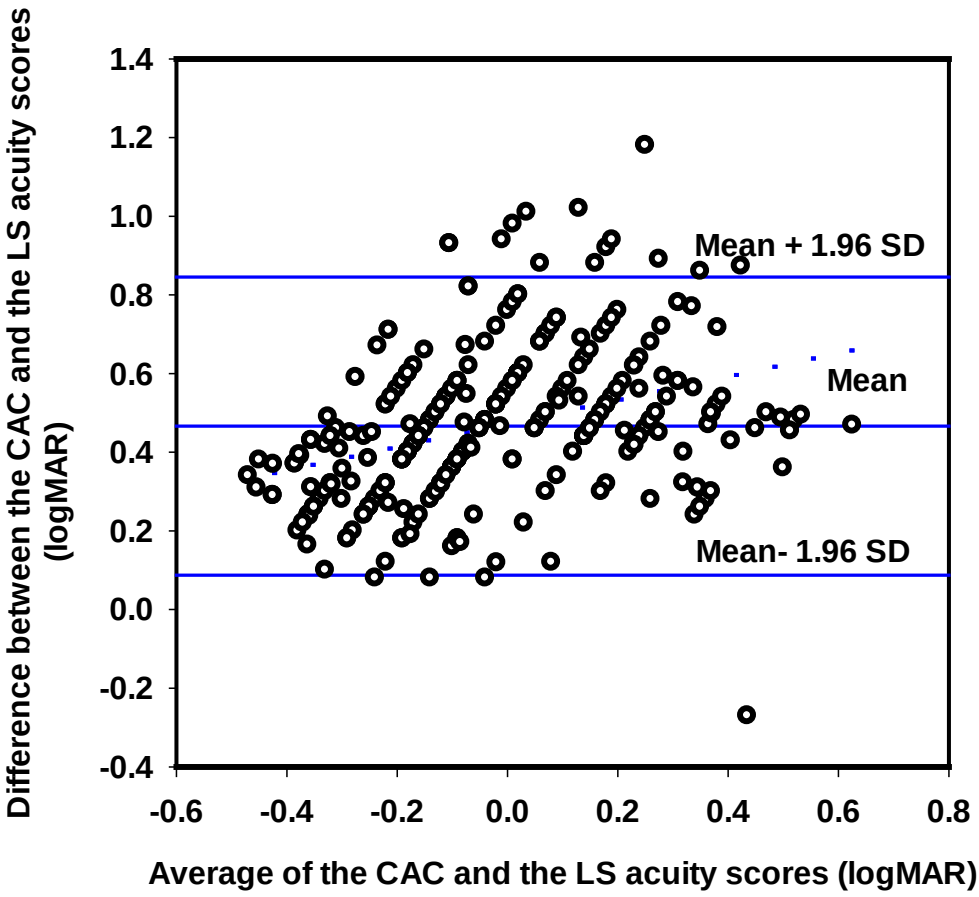

Figure 18 Bland-Altman chart demonstrating the agreement between acuities measured using Lea Symbols and acuities measured using the LS (all levels of focus and defocus measures are combined for the CAC and for the LS)

5.4.3. Effect of the spherical defocus

At lower levels of blur (1.0 D and 2.0 D) there was no clinically or statistically significant difference in acuity measurements between the adult gold standard ETDRS and LS charts, suggesting they produced equivalent results. However, at the highest level of spherical blur tested (3.0 D) there was a statistically significant difference between these two tests, with the Lea Symbols giving acuity measures 0.13 logMAR better than the ETDRS chart (Table 6). This difference borders on clinical significance based on the average test-retest reliability of VA measures of approximately 0.15 logMAR (Tsirlin, Colpa, Goltz, & Wong, 2015). There were statistically significant differences between the ETDRS chart and the CAC at all levels of blur. These were higher than the 0.31 logMAR difference found in the focused condition.

Similarly, there was a statistically significant difference between the average measures of the CAC and the LS chart for all of the blur levels. Again, the difference was higher than the difference found in the focused condition, and ranged from 0.43 to 0.52 logMAR across different blur conditions.

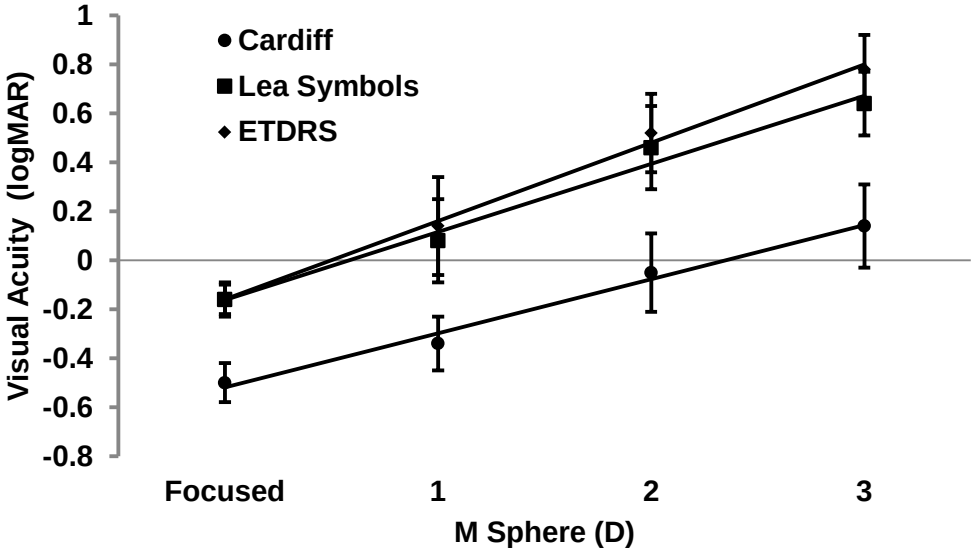

Figure 19. Mean visual acuities obtained from each acuity chart for different levels of spherical defocus. Error bars represent standard deviations.

Table 6. Mean differences between acuity levels obtained from different tests at different levels of spherical defocus. Negative values mean that the first chart in the comparison provided better acuity results. D=Dioptres

Charts combination compared	Mean difference (logMAR) ± SD					
	1D of defocus	*p*-value (Z)*	2D of defocus	*p*-value (Z)*	3D of defocus	*p*-value (Z)*
CAC and ETDRS	-0.48±0.18	<0.001 (-5.70)	-0.57±0.10	<0.001 (-5.77)	-0.63±0.20	<0.001 (-5.80)
CAC and LS	-0.43±0.14	<0.001 (-5.60)	-0.52±0.21	<0.001 (-5.64)	-0.49±0.19	<0.001 (-5.80)
LS and ETDRS	-0.05±0.09	0.31 (-1.01)	-0.05±0.12	0.183 (-1.33)	-0.13±0.10	0.002 (-3.09)

*Mann-Whitney U test

As expected, for all of the acuity charts there was a linear loss of visual acuity (increase in logMAR values) with the introduction of spherical defocus (Figure 17). The varying slopes of the fitted lines showing the effect of defocus on results from different acuity chart types suggest that the Cardiff Acuity Cards test was the most resistant and the ETDRS chart the most vulnerable to spherical defocus. The mean (SD) slopes across participants were: for the CAC, 0.22 ± 0.05 logMAR/D, for the LS, 0.27 ± 0.04 logMAR/D, and for the ETDRS, 0.32 ± 0.04 logMAR/D, with steeper slopes indicating a greater change in acuity per dioptre of a particular chart to blur. The slopes were statistically significantly different from one another (Kruskal-Wallis H, X^2=32.56, p<0.001). Post-hoc analysis with the Mann-Whitney U test revealed that each slope, for each chart, was different from the others (CAC VS LS, Z=-3.75, p=<0.001), (CAC VS ETDRS, Z=-5.07, p=<0.001), (LS VS ETDRS, Z=-3.13, p=0.002).

5.4.4. Effect of Astigmatic Defocus

Introduction of astigmatic defocus produced similar effects as that of the spherical defocus. In particular, there was a linear loss of acuity with increasing dioptric power (Figures 18,19, 20).

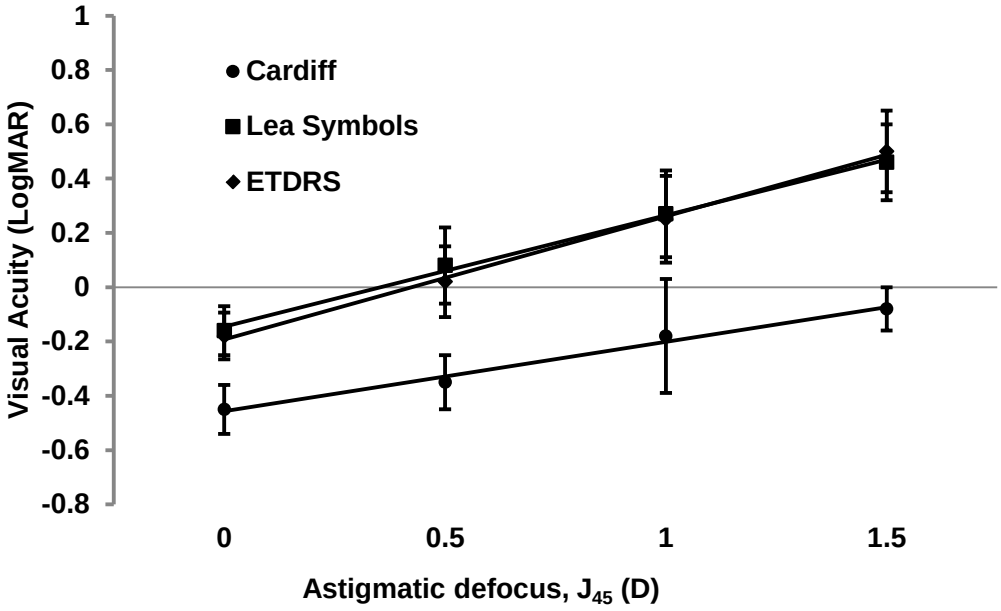

Figure 20. Mean visual acuity results for different levels of astigmatic defocus at 45 degrees orientation. Error bars represent standard deviations

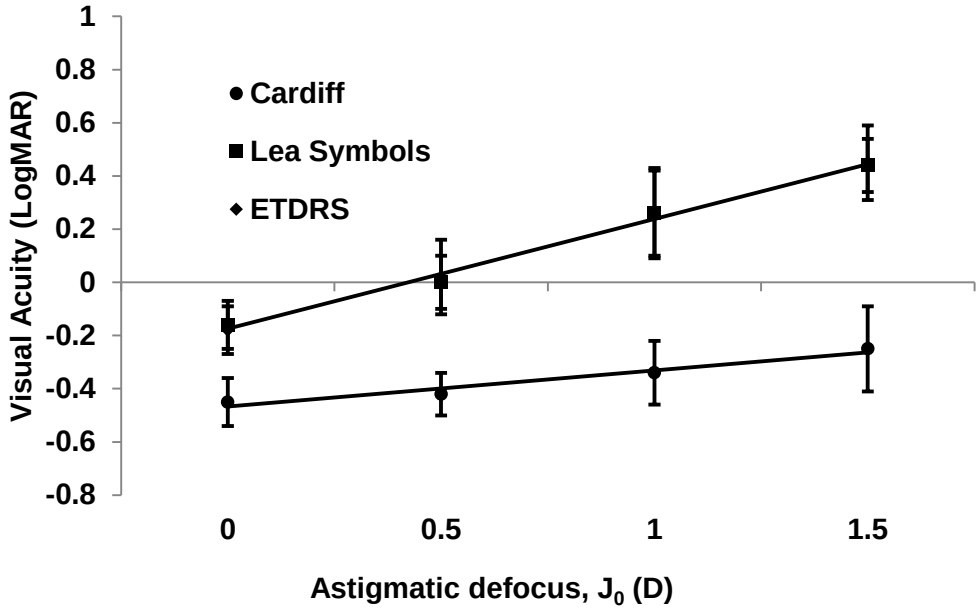

Figure 21. Mean visual acuity results for different levels of astigmatic defocus at 180 degrees orientation. Error bars represent standard deviations.

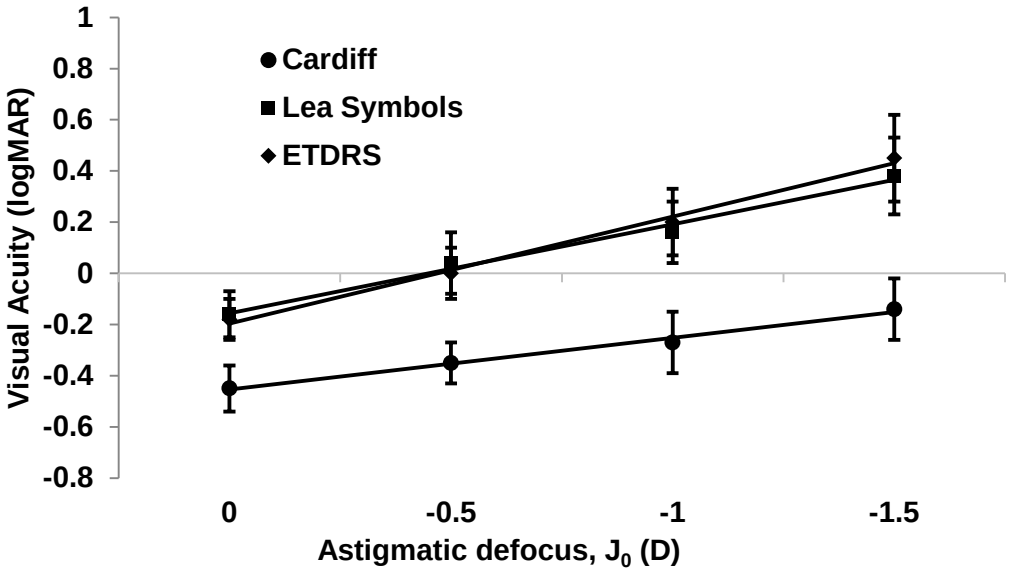

Figure 22. Mean visual acuities for different levels of astigmatic defocus at 90 degrees orientation. Error bars represent standard deviations

The mean change in slope (logMAR/D) across different orientations of astigmatic defocus ranged from 0.06 to 0.12 for the CAC, 0.17 to 0.20 for the LS, and 0.20 to 0.22 for the ETDRS (Table 5.2). The slopes of changes in VA due to astigmatic defocus were

significantly different from one another among the charts (Kruskal - Wallis H, $\chi 2$ = 87.12, p <0.001). The slope values suggest that the CAC test was less affected by astigmatic defocus, whereas the ETDRS chart was more affected by astigmatic defocus.

The orientation of the axis of astigmatic defocus had a significant effect on results obtained with the Cardiff Acuity Cards, where the 45 degrees orientation caused the maximum effect and the 180 degrees orientation caused the least effect. This means there was the highest reduction of VA while the orientation was 45 degrees but the least reduction while the orientation of the negative cylinder axis was at 180 degrees. There was no statistically significant effect of orientation of the axis of the astigmatic error on the results of the Lea Symbols test or the ETDRS chart (Table 7).

Table 7. Effect of orientation of astigmatic axis on the rate of visual acuity change with increasing astigmatic blur levels for the three different charts. Higher values indicate a greater effect of defocus on acuity.

VA Charts	Mean Rate (SD) (logMAR/J_0D)*			Significance, Kruskal-Wallis H
	45 degrees	90 degrees	180 degrees	
CAC	0.12 (0.04) Equates to 0.06 per DC*	0.10 (0.05) Equates to 0.05 per DC	0.06 (0.04) Equates to 0.03 per DC	X^2 =13.43, df=2 p=0.001
LS	0.20 (0.05) Equates to 0.1 per DC	0.17 (0.05) Equates to 0.08 per DC	0.20 (0.04) Equates to 0.10 per DC	X^2 =2.865, df=2 p=0.23
ETDRS	0.22 (0.05) Equates to 0.11 per DC	0.20 (0.06) Equates to 0.10 per DC	0.21 (0.04) Equates to 0.10 per DC	X^2 =0.93, df=2 p=0.62

**The conversion from rate of change of acuity per dioptre of JCC power to rate of change of acuity per dioptre of cylinder arises because a ±1D JCC has two dioptres of cylinder (prescription is +1.00DS / -2.00DC).*

5.5. Discussion

The main aim of this experiment was to determine the relationship between acuities measured with the Cardiff Acuity Cards and Lea Symbols and to compare those findings with those from the gold standard ETDRS chart. The moderate and statistically significant correlation between the CAC and the LS acuities suggests that results from the two tests within the same adult are meaningfully related to one another. Although the mean threshold

acuity obtained with the CAC was 0.3 log units different than that obtained with the Lea Symbols and ETDRS charts, the limits of agreement between all the tests were similar. This suggests that at least in focused conditions it may be possible to compare acuity measures between the charts as long as the 0.3 logMAR offset of the CAC is taken into account. This didn't appear to be true when the measures of VA under different conditions of defocus were incorporated in the analysis model. There was a considerably higher bias when the measures of different levels of defocus were incorporated. The regression analysis of the plot revealed that there was a proportional bias, which means that the bias between these two tests increased with increased reduced acuity. This indicated that a single correction value may not be sufficient in order to make the measures of the CAC and the LS comparable.

In fact, the acuity score obtained with the CAC was beyond the expected resolution limit of human retina, which is 0.50 arc minutes (Thibos, Cheney, & Walsh, 1987). Although the CAC was designed as a resolution task, our data suggests it is a detection task, and it is possible that the "disappearing" optotypes of the Cardiff Acuity Cards did not fully disappear into the background when the angular detail was below the limit of resolution. This would leave a luminance cue that the adult observers could use to identify which end of the card had the picture. It is unknown whether such luminance cues would attract the attention of a young child sufficiently to drive an eye movement that would allow for a preferential looking response to be observed. Even if the CAC optotypes did represent a detection task, blur would still affect results, as increasing blur would result in reduced contrast and this would make the optotypes more difficult to detect.

Our finding that CAC overestimates VA compared with the LS differs from that of a study by Woodhouse et al. (Woodhouse, Morjaria, & Adler, 2007), where they did not find any significant differences between Lea Symbols and CAC in a group of athletes who attended the Special Olympics (mean age: 24 ± 11.1 years) . The reason explaining the discrepancy between their findings and ours could be the fact that our study had fewer participants compared to theirs and also the strict inclusion criteria of our study, which employed a narrow range of best corrected acuities, compared with over 100 participants with intellectual disability with acuity range of -0.20 to 0.80 logMAR in the Woodhouse et al. study. However, Woodhouse et al. did explain that CAC underestimated VA for participants with poor acuity. This is consistent with our finding that the CAC is less affected by artificially induced refractive error than the Lea Symbols.

The difference between the CAC and other tests used in our study is likely to be related to the inherent design of the Cardiff Acuity Cards optotypes. Charman (2006) analysed the

spatial frequency profiles of Cardiff Acuity Cards and other similar vanishing optotypes and postulated that, unlike grating acuity cards, vanishing optotypes do not have distinct frequency patterns and do include a range of spatial frequencies. Furthermore, the frequency profile is not consistent across various pictures and varies according to the pictures used. Charman (2006) speculates, therefore, that these characteristics of CAC may interact differently with the optical and neural systems of humans and may provide different acuity results compared with other tests that have a fixed spatial frequency profile, such as Teller acuity cards and other high contrast letter acuity charts.

The results from Lea Symbols and ETDRS charts did not differ from one another in our study for the focused condition; however, they started to differ significantly only as spherical defocus was introduced. In the case of astigmatic defocus, the rates of change of acuity with defocus between Lea and ETDRS acuities were consistently statistically non-significant. Therefore, unless there is any other test that resembles the acuity measurements more closely than the LS with the ETDRS, LS seems to be a reasonable choice for assessing maximum visual acuity in children. This finding is consistent with previous studies (Dobson, Clifford-Donaldson, et al., 2009; Gräf et al., 2000).

There was a linear decrease in minimum angle or resolution with an increasing amount of both spherical and cylindrical defocus. This resulted in the reduction in visual acuity per dioptre of spherical defocus ranged from 0.22 to 0.32 on average, which was higher than visual acuity reduction with per dioptre increase in astigmatic defocus (range 0.03 to 0.11 logMAR). This finding was similar to that reported in the literature (Rabin, 1994). The highest degradation of acuity was for the ETDRS chart for both the spherical and astigmatic defocus. Our finding of reduction in acuity per dioptre of astigmatic defocus for ETDRS is slightly less than in the study by Atchison & Mathur, (2011) on the effect of astigmatic blur strength (equivalent to JCC power) on high contrast acuity, which was 0.34±0.05 logMAR/D. The slope values for astigmatic defocus across different orientations differed considerably across various charts. The nature of the optotype design for the Cardiff Acuity Cards could be a possible factor for this test's high resistance to degradation with increasing astigmatic defocus. In particular, the combination of multiple spatial frequency content of the optotypes (Charman, 2006) is likely to render them less susceptible to blur than the optotypes used in other charts. Furthermore, detection acuity is less sensitive to defocus than recognition acuity (Thorn & Schwartz, 1990), which is why recognition acuity tests are used as soon as children have the cognitive ability to perform them accurately. The significant impact of orientation of the astigmatic axis on the CAC but not on the LS and the ETDRS could be due to the fact that the majority of pictures in the CAC predominantly comprise horizontal and vertical borders which are altered differently by astigmatic defocus that is primarily along 90

and 180 degree meridians as compared to astigmatic defocus that is along 45 and 135 degree meridians.

While our study is unique in many aspects, we accept that it is not without limitations. We recruited adult participants for this study because we wanted to find how the acuity tests performed when factors such as attention and cognition were not limited by incomplete development of central nervous system processes that might have had a variable influence on our results. However, as multiple testing was carried out with the same test chart, learning or fatigue effects might have influenced our findings. Moreover, as mentioned by Little et al., (2012) children tend to give up easily when they approach threshold; however, adults use their maximum effort to reach the threshold level. Therefore, the overestimation of visual acuity we report for the adult tests on the Cardiff Acuity Cards may not be as pronounced when children are examined. Nevertheless, a sub-group analysis of twenty five 4.5-year-old children on whom we were able to conduct both the CAC and LS revealed that the CAC overestimates VA by two and half logMAR lines (Chapter 6, Section 9.1.1).

Furthermore, we did not incorporate measures to control accommodation of the participants, unlike a previous study (Little et al., 2012), even though we made sure that the luminance and illumination levels of the test charts were consistent during testing. Also, we allowed our participants a relatively short duration for adaptation to the defocus (30 seconds) which might not have been a sufficient time for the induced spherical or cylindrical defocus to mimic the real situation where defocus has developed over time.

Notwithstanding these limitations, our study provides strong evidence that Cardiff Acuity Card results can be related to Lea Symbols in the absence of blur and other cognitive factors by the inclusion of a correction factor. We propose the correction factor to be 0.30 logMAR. When such a correction factor is used, Cardiff cards can be used in studies involving longitudinal development of visual function. Cardiff Acuity Cards appear to be less affected by significant amounts of defocus, which may reduce their ability to detect children with significant refractive error until the acuity reductions are considerable.

5.6. Conclusion

This study compared the threshold acuity values of Cardiff Acuity Cards and Lea Symbols with the gold standard ETDRS chart under focused and defocused conditions. The moderate correlation between the CAC and the LS proves that there is a reasonable relationship between the two tests. The three vision charts were differentially susceptible to defocus,

which implies that charts interact differently with different levels of blur. The CAC were highly resistant to both the spherical and astigmatic defocus. Our study contributed to the existing knowledge that the Lea Symbols are as similarly affected by defocus as the gold standard ETDRS chart and that Lea Symbols should be used as a screening tool with children as soon as they it is feasible to use them. It should be noted that current paediatric visual acuity tests suffer from an inherent difficulty of a compromise between testability and accuracy. However, a visual acuity testing system that cannot be used (poor testability) has little place in paediatric vision assessment, and a sacrifice of accuracy is inevitable when it is important to detect significant problems at an early stage in growing children. Overall, these data suggest that, where cognitive and visual development is incomplete, acuity measurements made using the CAC and Lea Symbols are moderately correlated with one another. However, the CAC overestimates acuity by approximately three lines and this overestimation needs to be accounted for in any comparison between the two tests. The increases in overestimation with increasing mean visual acuity between the two tests indicated that an exact correction factor is difficult to determine when the CAC is to be used in population with high potential of developing abnormal visual function/astigmatism. Furthermore, this finding provided some evidence that raw measures of visual acuity obtained with age appropriate tests may not be suitable to study longitudinal development of visual acuity. This led us to the concept of normalisation of the data that has been discussed in section 4.7.

Chapter 6. The development of visual acuity, stereopsis and global motion perception from 2 to 4.5 years of age

This chapter presents results relating to the visual development of the whole CHYLD study cohort from 2 to 4.5 years of age. Raw (i.e., not normalized) data collected at 2 and 4.5 years of age are presented alongside adult data for each test. Analyses of the raw and adult-normalized data from are then presented. It was possible to collect data from a subset of children at the 4.5-year assessment using both the 4.5-year and 2-year tests. These data, which have a bearing on the relationship between the 4.5- and 2-year tests and build upon the results presented in Chapter 5, are presented at the end of the chapter.

6.1. Summary of the raw data

The means and medians for raw (not normalized) visual acuity, stereopsis and motion coherence thresholds at 2 and 4.5 years of age are presented in Table 8. The adult data that were used for normalization (described in Chapter 4 section 7) are also presented.

Table 8. Mean and median adult and child thresholds for visual acuity (VA), stereopsis and motion coherence (MCT) for each of the tests used within the study. OKN- Optokinetic nystagmus, SD- Standard deviation, IQR- Interquartile range.

Visual Function		Adult Thresholds (N=15)		Child Thresholds	
		Mean (SD)	**Median (IQR)**	**Mean (SD)**	**Median (IQR)**
Tests for 2-year-olds	**Binocular VA (Cardiff) LogMAR**	-0.46 (0.10)	-0.48 (-0.22 to -0.12)	0.06 (0.15)	0.00 (-0.10 to 0.10)
				N= 310	
	Lang II Stereoacuity (Seconds of arc)	200 (0.00)	200 (0.00)	373.68 (204.50)	400 (200 to 400)
				N= 302	
	Frisby stereoacuity (Seconds of arc)	22.70 (7.03)	20.00 (0.00)	332.86 (166.90)	300 (170 to 340)
				N= 203	
	MCT (OKN) %	5.72 (1.38)	5.88 (4.66 to 6.70)	42.34 (14.20)	41.07 (32.12 to 50.41)
				N= 335	
Tests for 4.5-year-olds	**Binocular VA (Lea symbols) LogMAR**	-0.14 (0.10)	-0.16 (-0.22 to -0.12)	0.07 (0.11)	0.06 (0.00 to 0.10)
				N= 257	
	Stereo Fly stereoacuity (Seconds of arc)	29.60 (20.36)	25.00 (20 - 32)	85.97 (69.12)	63.00 (50 to 100)
				N= 324	
	MCT (behavioural) %	17.85 (6.11)	16.25 (14.5 - 22.25)	51.11 (20.49)	53.25 (34.00 to 66.75)
				N= 333	

It is evident from Table 8 that the number of children that performed each test is different. This does not necessarily depict the testability of the test but rather determines the priority of the test that had to be conducted according to the CHYLD study protocol. The global motion perception test was attempted first as it was the most attentionally demanding. This test was followed by the visual acuity and stereopsis tests. Longitudinal analysis of a particular visual function was conducted in children who performed the particular test at both ages. For instance, children who performed the global motion perception test at 2 years but not at 4.5 years were excluded from analysis. The data that I present here partially overlaps with that of the two PhD student colleagues some of which has been published earlier (Chakraborty et al., 2015; Yu et al., 2013). However, the research questions for each of the PhD projects were unique even though there was overlap in the assessed children.

6.2. Characteristics of the children assessed at both 2 and 4.5 years

A total of 355 children were assessed at age 2 years and at age 4.5 years. Characteristics of these children are presented in Table 9.

Table 9. Gender, risk factors and glycaemic status for children enrolled in this study.

Characteristics	**Frequency (%)**
Gender	
Male	186 (52.4)
Female	169 (47.6)
Primary Risk Factors	
Preterm	112 (31.5)
Small for gestational age (SGA)	55 (15)
Large for gestational age (LGA)	35 (10)
Infants of diabetic mothers (IDM)	144 (40.5)
Others	11 (3)
Number of risk factors	
1 risk factor 2 risk factors 3 risk factors	150 (42.2) 193 (54.4) 12 (3.4)
Glycaemic status	
Hypoglycaemic Euglycaemic	193 (54.4) 162 (45.6)

6.3. Prevalence of eye and vision disorders at age 2 years and age 4.5 years

Detailed optometric screening of the 355 children at both age 2 years and 4.5 years revealed a higher prevalence of visual disorders at age 4.5 years. Having eye and vision disorders was noted if binocular visual acuity was ≤ 0.50 logMAR at 2 years or BVA <0.30 logMAR at 4.5 years or if abnormal binocularity or ocular pathology was detected at either age (see Chapter 4, sections 1.1.5 and 2.1.5 for referral criteria). Of the children at age 4.5 years, 13.5% (48) had eye and vision problems. However, only 8.4% of the children at age 2 years were detected as having eye and vision problems. Out of the 48 children who were diagnosed at age 4.5 years, 3 children had already been detected at age 2 years and were already under the care of an eye care provider. The prevalence of eye and vision disorders at 2 years and 4.5 years is presented in Table 10.

Table 10. Prevalence of eye and vision disorders at age 2 years and age 4.5 years. Some children had more than one condition. Refractive error was not measured at 4.5 years.

	2 years, N (%)	**4.5 years, N (%)**
Visual acuity outside normal limits	6 (1.7)	42 (13.5)
Refractive errors	14 (4.0)	-
Strabismus	9 (2.5)	5 (1.4)
Ocular pathology	2 (0.05)	1 (0.02)

Out of the 42 children who had visual acuity outside normal limits at 4.5 years of age, 31 had reduced vision either in one or both eyes. The rest were uncooperative for the use of any acuity test. The prevalence of strabismus was higher at age 2 years (Table 10). Out of the nine strabismic children (7 esotropes and 2 exotropes) who were diagnosed at age 2 years, two were under the care of an eye care professional and were still undergoing treatment at age 4.5 years, four developed normal binocularity at age 4.5 years and three had not attended the recommended treatment and were left untreated. Two new children, who were not detected as having strabismus at age 2 years, had strabismus at age 4.5 years.

6.3.1. Visual status of children at 4.5 years who had poor acuity at 2 years and vice versa

Table 11 shows the binocular visual acuity of the children at 4.5 years who had binocular visual acuity outside normal limits at age 2 years. Except for one child, all of the children had developed acuity within normal range by age 4.5 years.

Table 11. Binocular VA of children at age 2 years and at age 4.5 years who were outside normal limits at age 2 years. (BVA- Binocular Visual Acuity, CAC - Cardiff Acuity Cards, LS – Lea Symbols)

BVA at 2 years (logMAR) with the CAC	BVA at 4.5 years (logMAR) with the LS
1.20	0.10
0.70	0.26
0.50	0.10
0.50	0.00
0.50	0.26
0.50	Unable to assess with LS 0.00 (with CAC)

Similarly, we were interested to observe the visual acuity status of children at 2 years who were outside normal limits at 4.5 years. Out of the 42 children who had abnormal visual acuity at 4.5 years, we were unable to assess BVA in 7 children while they were 2 years of age. One child had visual acuity outside normal range. The remaining 34 children had BVA within normal limits at 2 years of age.

6.4. Development of binocular visual acuity from 2 years to 4.5 years

Presenting binocular visual acuity was successfully measured in 223 children at both the ages of 2 and 4.5 years. The median (IQR) acuity of 0.00 (-0.08 to 0.10) logMAR at 2 years was not significantly different from the median acuity of 0.06 (0.00 to 0.10) logMAR at 4.5 years (Figure 23) (*Z*= -1.866, *p*=0.062, Wilcoxon signed-rank test).

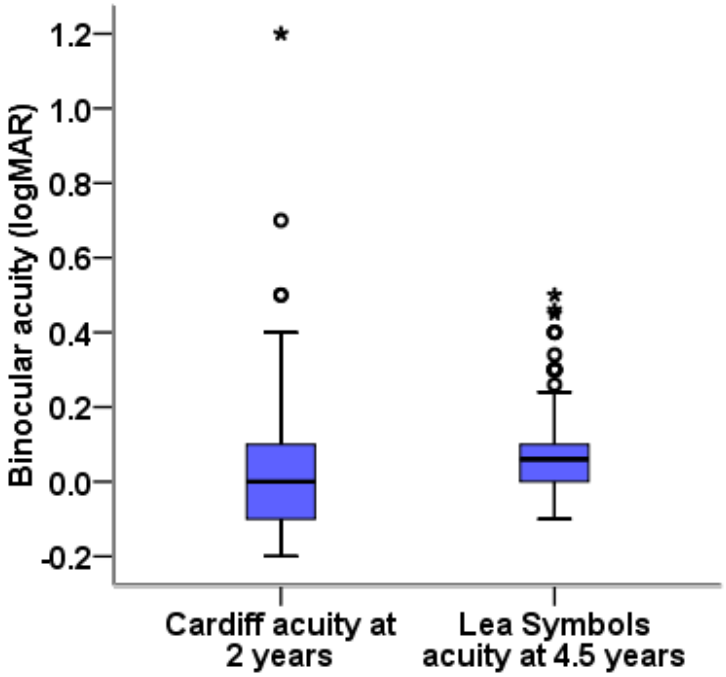

Figure 23. Raw binocular visual acuity at age 2 years and 4.5 years (N=223). Here, and for all subsequent figures, the upper and lower ends of the box represent the 1st and the 3rd quartiles. The solid line inside the box represents the median value. The end of the top whisker represents the maximum value and the end of the bottom whisker represents a minimum value. The circles represent outliers which were either 1.5 times IQR or more above the third quartile or 1.5 times IQR or more below the 1st quartile. The stars represent outliers which were either 3 times IQR or more above the third quartile or 3 times IQR or more below the 1st quartile.

The four outliers for the Cardiff acuity test at 2 years had raw score acuities of 1.2 logMAR (marked by the star symbol), 0.70 logMAR (the upper circle), and 0.50 LogMAR each (lower circles, overlapped). The acuity values for the outliers at 4.5 years ranged from 0.26 logMAR to 0.50 logMAR.

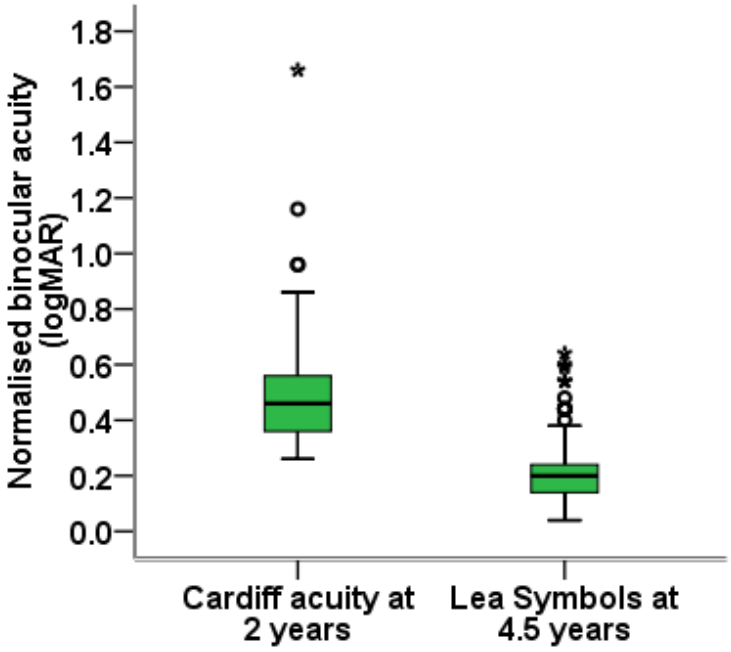

Figure 24. Normalized binocular acuity at 2 years and 4.5 years (N=223). Error bars and outliers are shown as in figure 23.

Figure 24 shows the acuity data normalized to adult values. These normalized acuity data show that visual acuity does improve from age two years to age four-and-a-half years. At 2 years the acuity was one and half octaves (0.46 logMAR) worse than adults, whereas at 4.5 years the acuity was less than an octave worse than adults (0.20 logMAR). This change in normalized acuity over the duration of 2.5 years was statistically significant (Z= -12.85, p<0.05, Wilcoxon signed-rank test). The improvement in binocular visual acuity from 2 years to 4.5 years was 56%.

6.5. Development of stereopsis from age 2 years to age 4.5 years

At age 2 years, stereopsis was assessed using the Frisby stereo test as well as the Lang stereo test, whereas only the Fly stereo test was used at age 4.5 years. The Frisby stereo test was the test of choice, but in cases where children did not comply, the Lang stereo test was used. One hundred and ninety children performed the Frisby stereo test at 2 years and the Fly stereo test at 4.5 years. Median stereo acuities, achieved using the different tests, are presented in Table 8. A Wilcoxon signed-rank test indicated that Fly stereoacuity thresholds at 4.5 years were statistically significantly better than Frisby stereoacuity thresholds at 2 years (Z= -11.60, p<0.001).

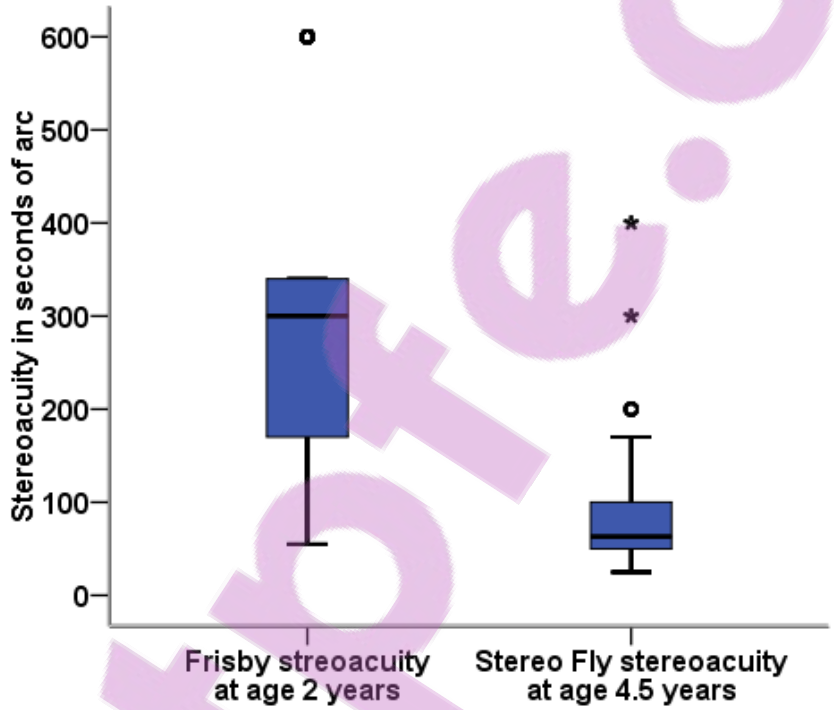

Figure 25. Raw stereoacuity at age 2 years (Frisby) and at age 4.5 years (Fly Stereo test), (N=190) Boxes and whiskers are shown as in figure 23.

Figure 25 shows the stereopsis data normalized to adult values. The median performance of children at 2 years was a factor of 13 (7.5 to 15) worse than adult values. However, the median stereopsis at 4.5 years was just a factor of 2 (1.66-3.33) worse than the adult values. This indicated an 84% increase in stereopsis. This change was statistically significant (Z= -11.80, p <0.05, Wilcoxon signed-rank test).

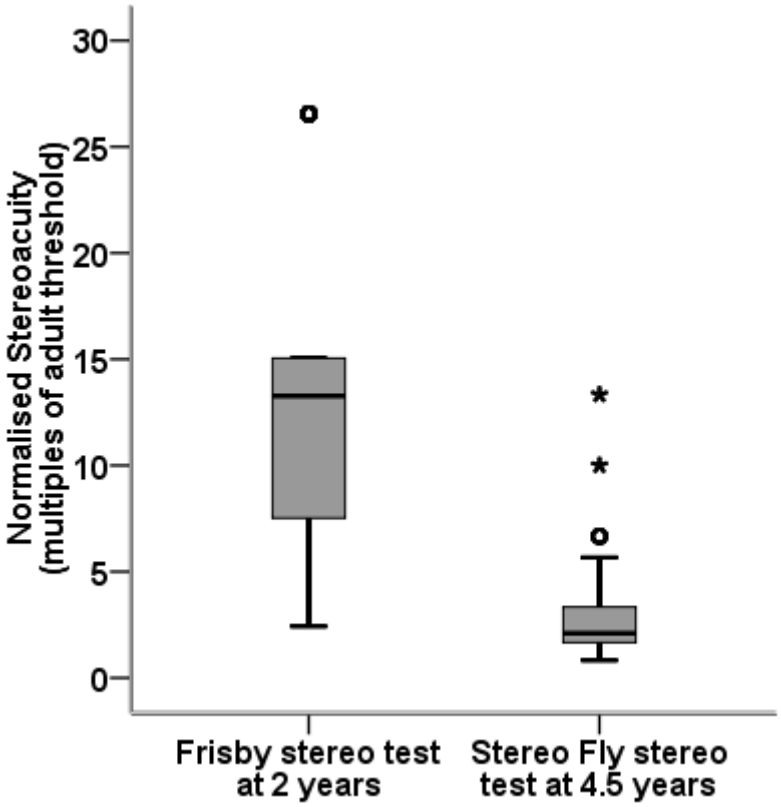

Figure 26. Development of stereoacuity from age 2 years to 4.5 years (N=190). Boxes and whiskers are shown as in figure 23.

Similarly, 278 children underwent the Lang stereo test at 2 years and the Fly stereo test at 4.5 years. There was a significant difference in the median (IQR) stereoacuity between the measurements made at 2 and 4.5 years of age: 400 seconds of arc (200" to 400") versus 63 seconds of arc (50" to 100") (Z=-14.35, p= <0.001, Wilcoxon signed-rank test). In contrast, normalized data showed that there was a small but statistically significantly better median (IQR) performance at 2 years with the Lang stereo test than at 4.5 years with the Fly stereo test: 2.00 (1.00 to 2.00) versus 2.1 (1.66 to 3.33) (Z= -7.5, p<0.05, Wilcoxon signed-rank test). The Lang stereo test did not measure true threshold in adults due to a ceiling effect; the smallest threshold measurable (200 second of arc) was well above the actual threshold for adults. Hence, the normalized values obtained using the Lang stereo test should be interpreted cautiously.

6.6. Development of global motion perception from age 2 years to age 4.5 years

The distribution of global motion coherence thresholds at 2 years is shown in Figure 27 and that for 4.5-year-old children is shown in Figure 28. The Kolmogorov Smirnov goodness-of-fit test was significant for both distributions ($p<0.05$), indicating that both datasets were not normally distributed. In total, 315 children (at 2 years and 4.5 years) performed the global motion perception test.

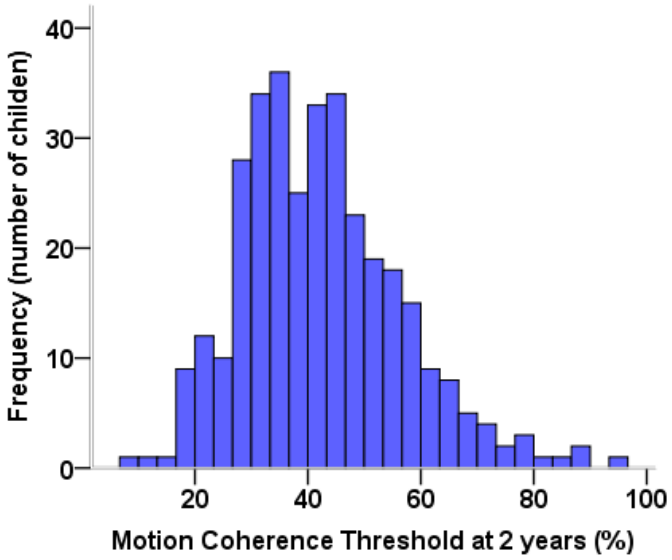

Figure 27. Distribution of raw motion coherence thresholds at 2 years

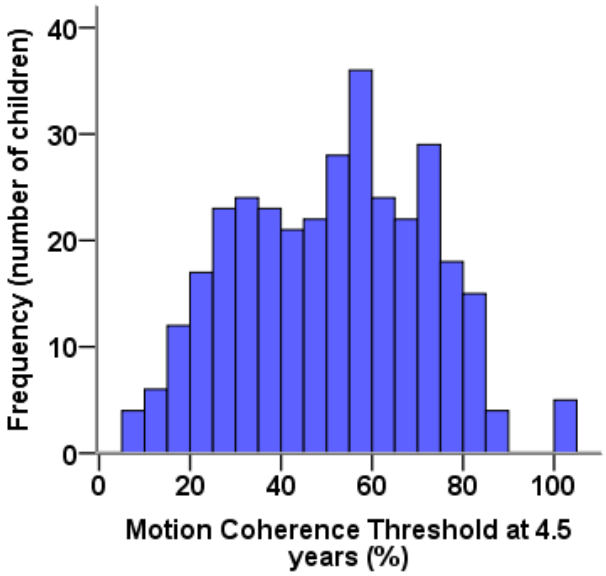

Figure 28. Distribution of raw motion coherence thresholds at 4.5 years

Figure 28 illustrates the raw motion coherence thresholds at 2 years and 4.5 years of age.

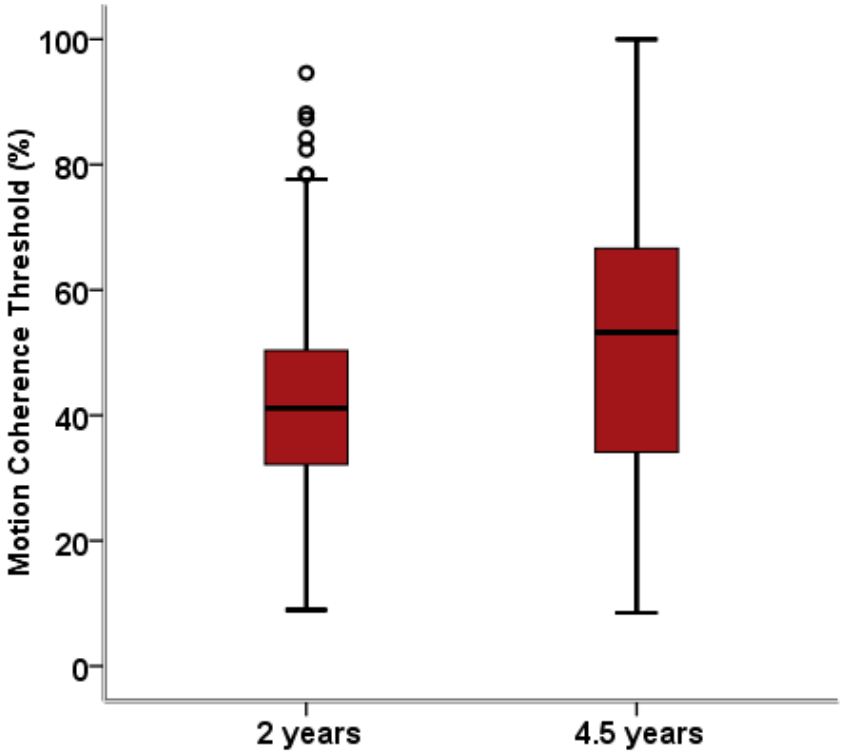

Figure 29. Raw motion coherence thresholds at age 2 years and age 4.5 years (N=315). Boxes and whiskers are shown as in figure 23.

The raw motion coherence thresholds at age 4.5 years were statistically significantly worse than those measured at age 2 years, p= <0.001, Z=-6.07 (Wilcoxon signed-rank test). (Figure 29) This might seem to be unexpected but it must be remembered that different age-appropriate tasks and protocols were used to assess motion coherence thresholds at 2 and 4.5 years of age. The importance of the difference in testing protocols at 2 and 4.5 years was apparent when the motion coherence thresholds were normalized to adult values. For the normalized data, the children performed significantly better when they were 4.5 years of age than when they were 2 years of age (Figure 30).

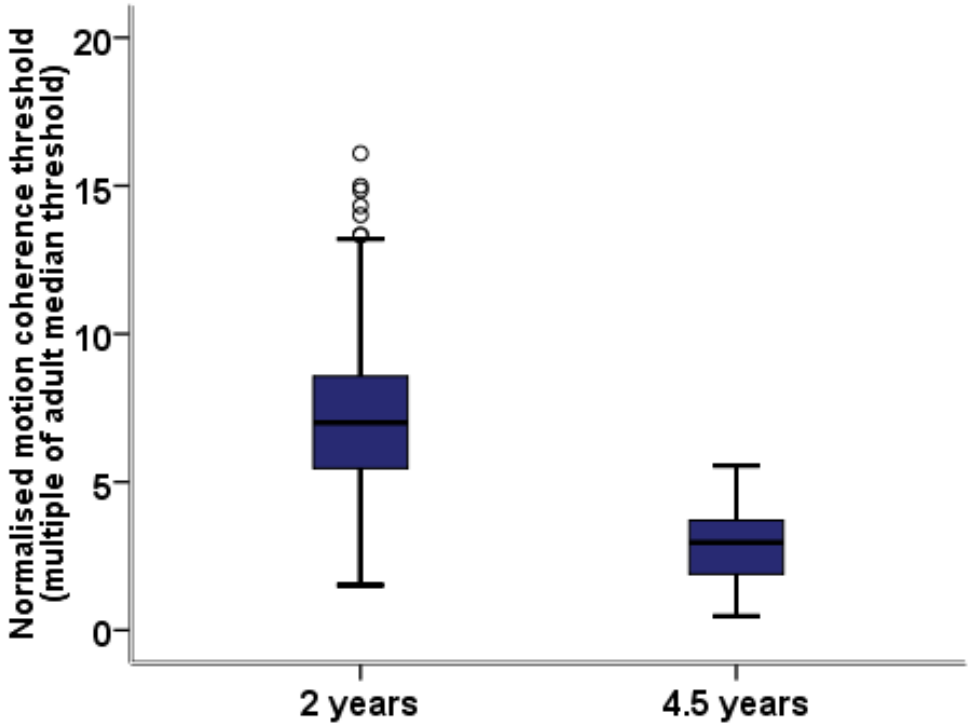

Figure 30 Development of global motion perception from age 2 years to age 4.5 years. Boxes and whiskers are shown as in figure 23.

There was an improvement of 2 octaves in normalised motion coherence threshold from 2 years to 4.5 years and this was statistically significant (Wilcoxon signed-rank test, $p < 0.001$, $Z = -15.23$) .

6.7. Summary of development of normalized visual function from age 2 years to age 4.5 years

In summary, the normalized values showed a clear trend of significantly improved performance of visual function with age (Figure 31). However, none of the visual functions reached adult levels by 4.5 years. The greatest improvement was for stereopsis followed by global motion perception and visual acuity. Visual acuity improved by 0.7 octaves. Stereoacuity improved by 5.5 octaves and global motion perception improved by 2 octaves.

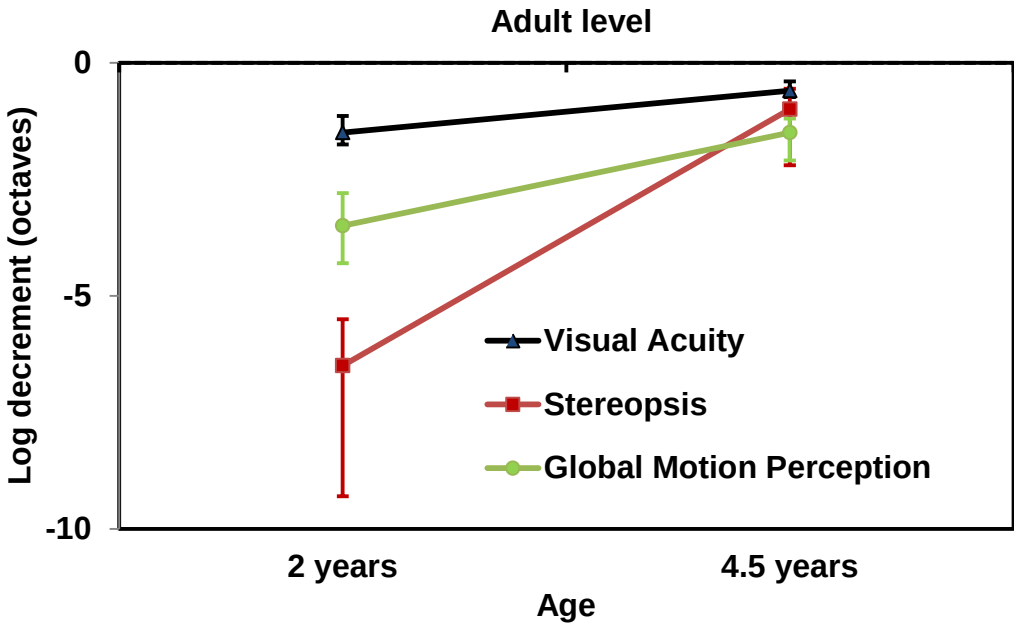

Figure 31. The development of visual acuity, stereopsis and global motion perception from 2 to 4.5 years of age. Data points represent median normalized values relative to adults and error bars represent IQR. Stereoacuity was measured using the Frisby stereo test at age 2 years and the Fly stereo test at 4.5 years. Data are shown as log decrement (in octaves) relative to adult threshold to allow for a direct comparison across different visual functions. This plot is based on a previous article which describes on the maturation of infant vision. (Teller, 1997) Octave represent doubling.

6.8. Influence of gender on the development of normalized visual functions

Gender had no effect on the development of any of the normalized visual functions (Table 12).

Table 12. Median change in normalized visual functions according to gender (binocular visual acuity is denoted in logMAR, stereoacuity in seconds of arc and global motion perception in percent coherence). The Mann-Whitney U test was used to test for differences between females and males.

Visual functions	Median				Significance
	Male	N	Female	N	
Binocular visual acuity	0.32 (0.20 to 0.42)	122	0.30 (0.22 to 0.36)	101	*p* = 0.59 Z = -0.52
Stereopsis					
Lang vs. Stereo Fly	-0.66 (-1.33 to 0.13)	141	-0.58 (-1.33 to 0.16)	137	*p* = 0.98 Z= -0.01
Frisby vs. Stereo Fly	11.71 (5.85 to13.97)	99	11.71 (5.88 to 21.21)	91	*p* = 0.95 Z = -0.05
Global motion perception	4.21 (2.66 to 5.93)	169	4.20 (2.29 to 5.81)	146	*p* = 0.82 Z = 0.85

6.9. The relationships between measures of visual function at age 2 years and at age 4.5 years.

The relationships between visual functions measured at 2 years and visual functions measured at 4.5 years using age-appropriate tests were explored. This was done to understand whether the measures at 4.5 years could be predicted based on measures obtained at age 2 years.

6.9.1. The relationship between binocular visual acuity at age 2 years and at age 4.5 years

Raw measures of binocular Cardiff Acuity Cards at 2 years and raw measures of binocular Lea Symbols test acuity at 4.5 years were weakly but significantly positively correlated (Spearman's rho= 0.20, p=0.003, N=223) (Figure 32). The correlation remained unchanged after the acuity values were normalized to adult values.

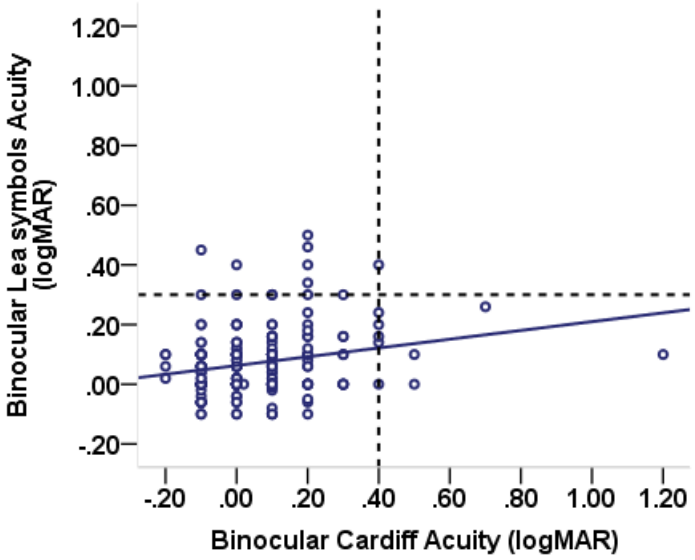

Figure 32. Scatterplot showing the distribution of binocular acuities at 2 years (Cardiff Acuity Cards, x-axis) and 4.5 years (Lea Symbols, y-axis). Dotted lines represent the upper limits of published norms for each test, from Becker, Hübsch, Gräf, & Kaufmann (2002) and Adoh and Woodhouse (1994). Here, and for the subsequent scatter plots, the solid line represents the line of best fit also known as the trend line.

6.9.1.1. Relationship between measures of visual acuity using the Cardiff Acuity Cards and Lea Symbols in 4.5 year old children

A small subset of 4.5-year-old children (N=25) completed both the CAC and LS tests. A moderately strong positive correlational relationship (Figure 33) was observed between these two tests (rho= 0.53, *p* = 0.007). However, similar to the results in adults (Chapter 5) CAC overestimated visual acuity by approximately two-and-a-half (2.5) logMAR lines.

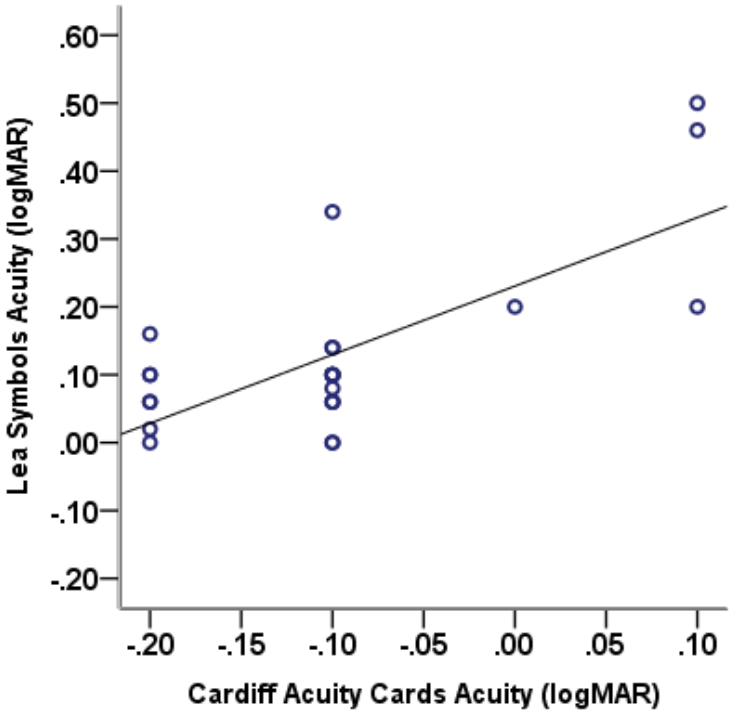

Figure 33. The relationship between measures of visual acuity made using the CAC and LS in 4.5-year-old children (N=25)

6.9.2. Relationship between measures of stereopsis at age 2 years and at age 4.5 years.

There was no correlation between Frisby stereoacuity at 2 years and Fly stereoacuity at 4.5 years (Spearman's rho=0.07, p=0.33, N=190). In contrast, there was a statistically significant but weak positive correlation between Lang stereoacuity at 2 years and Fly stereoacuity at 4.5 years (Spearman's rho= 0.23, p=0.001, N=278). This relationship is shown in Figure 34. Normalized stereoacuity (Lang at 2 years versus Fly stereo test at 4.5 years values) also yielded a weak but statistically significant correlation.

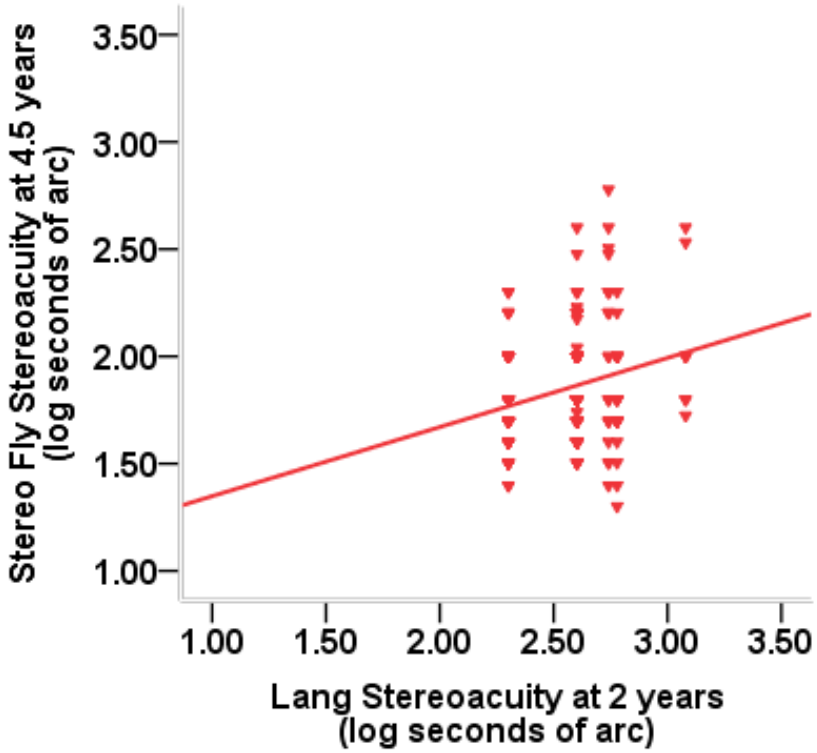

Figure 34. Relationship between measures of raw stereoacuity at 2 (Lang) and 4.5 (Fly) years of age. Data are shown in log seconds of arc

The weak correlation and the limited range over which the Lang stereo test assesses stereopsis (2.3 to 3.0 log seconds of arc) suggests that there is no clinical value in trying to predict how stereopsis might develop based on measurements at 24 months of age. Moreover, the lack of correlation between the Frisby stereo test and the Fly stereo test suggests that stereopsis cannot be predicted from 2 years to 4.5 years using these tests.

6.9.3. The relationship between measures of global motion perception at age 2 years and at age 4.5 years.

There was no statistically significant correlation between motion coherence thresholds at 2 years and 4.5 years (Spearman's rho=0.024, p=0.67) (N=315) (Figure 35). Correlation between the normalized threshold values at these two ages yielded exactly the same correlation coefficient as the raw measures.

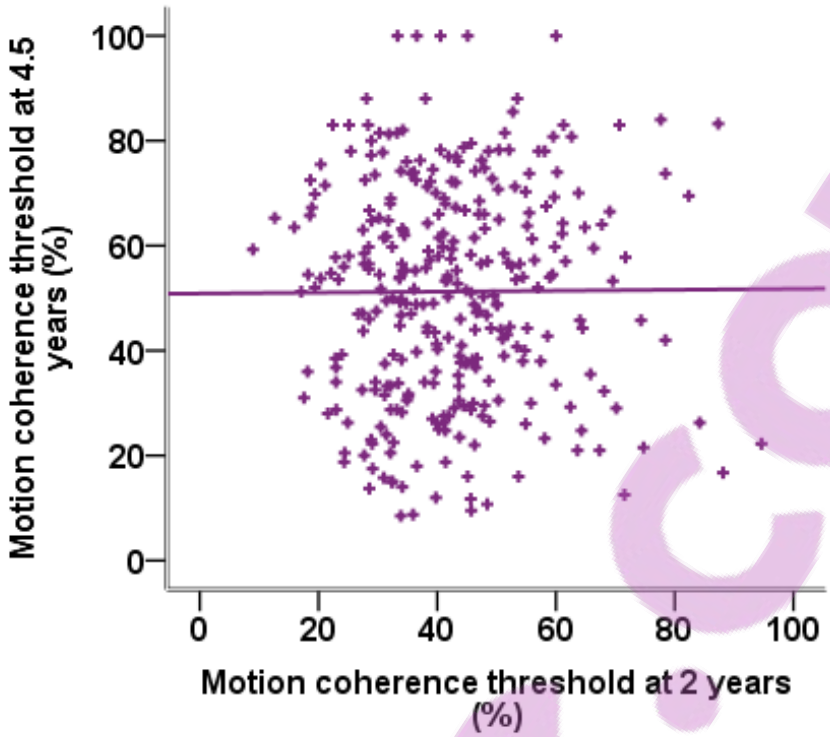

Figure 35. The relationship between motion coherence thresholds at 2 years and 4.5 years (N=315)

6.9.4 Summary of the relationships between visual function measures at 2 years and 4.5 years.

Visual acuity and stereopsis measures were reliably (but weakly) correlated at 2 and 4.5 years of age. Stereopsis showed the correlation when the Lang test was used a 2 years but not when the Frisby test was used at 2 years. Global motion perception measured at 2 years was uncorrelated with global motion perception measured at 4.5 years. Overall, measures of vision made at 2 years did not predict visual function at 4.5 years in this cohort of children.

Chapter 7. The effect of neonatal hypoglycaemia and its risk factors on the development of visual acuity, stereopsis and global motion perception

This chapter reports results relating to the effect of neonatal hypoglycaemia on visual development from 2 to 4.5 years of age within the CHYLD study cohort. Additional results on the effects of individual and multiple risk factors for neonatal hypoglycaemia on the development of visual function are also presented. All analyses were conducted on data normalized to adult values. This allowed for developmental changes in visual function to be isolated from the effects of using different age-appropriate tests within the 2- and 4.5-year assessments (Chapter 6). Part of the data that is presented in this chapter have been used in previous studies in order to answer different research questions to that described in this thesis.(Chakraborty et al., 2015; Yu et al., 2013)

7.1. Effect of neonatal hypoglycaemia on the development of visual functions

As mentioned in Chapter 4, children who had heel-prick blood glucose measurements within 48 hours of birth of <2.6mmol/L were considered as having hypoglycaemia. Out of the 355 children who were longitudinally followed up until 4.5 years, 193 (54.4%) had experienced hypoglycaemia during the neonatal period. Of the males, 46% (87) had experienced hypoglycaemia, and of the females, 63% (106). The Chi-squared test revealed that females had a significantly higher incidence of NH than males: $X^2(1) = 9.077$, $p = 0.003$.

7.1.1. Effect of neonatal hypoglycaemia on the development of binocular visual acuity

Habitual BVA both at 2 years of age and at 4.5 years of age was measured in 223 children in the cohort. There was no statistically significant effect of the presence or absence of NH on the development of binocular visual acuity (Table 15).

Table 13. Median (IQR) values of normalized BVA for the hypoglycaemic and euglycaemic groups of children.

	Hypoglycaemic (N=116)	**Euglycaemic (N=107)**	**Significance, Mann-Whitney U Test**
Normalized BVA at 2 years (logMAR)	0.47 (0.46 to 0.56)	0.46 (0.36 to 0.56)	
Normalized BVA at 4.5 years (logMAR)	0.20 (0.10 to 0.24)	0.20 (0.14 to 0.24)	Z = - 0.398, *p*=0.69
Change from 2 to 4.5 years (logMAR)	0.32 (0.22 to 0.38)	0.30 (0.20 to 0.42)	

7.1.2. The effect of neonatal hypoglycaemia on the development of stereopsis

Stereoacuity was measured in 203 2-year-olds with the Frisby stereo test and 324 4.5-year-olds with the Fly stereo test; 190 children had measures on both of these tests. In addition, 278 children completed the Lang stereo test at 2 years and the Fly stereo test at 4.5 years.

The change in stereoacuity measured using the Frisby stereo test at 2 years and the Fly stereo test at 4.5 years was not significantly different between the hypoglycaemic and euglycaemic groups (Mann-Whitney U test, Z= -0.482, *p*=0.63) . The change in stereoacuity measured using the Lang test at 2 years and the Fly stereo test at 4.5 years was also not significantly different between the two groups (Z= -0.257, *p*=0.80) thresholds (Figure 36).

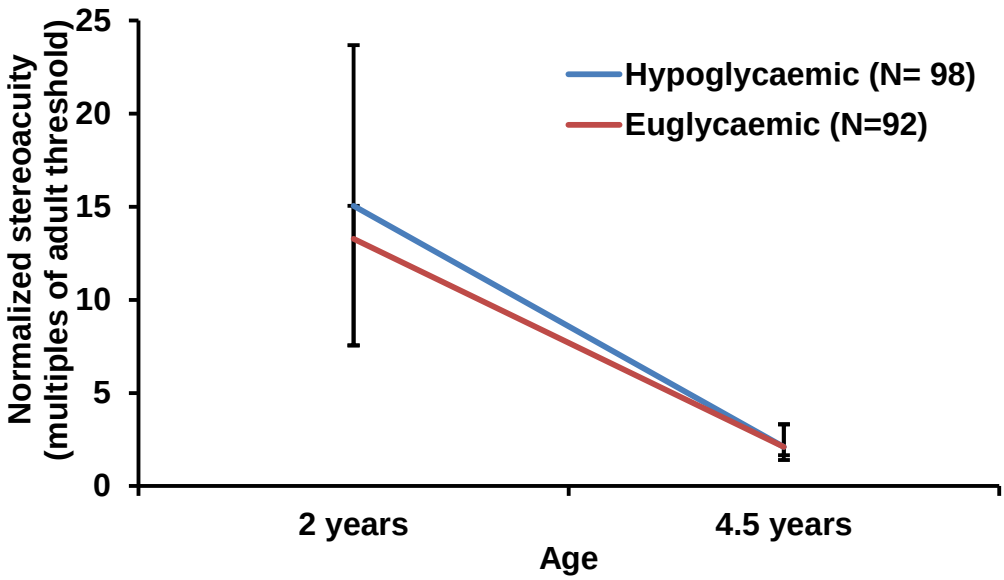

Figure 36. Developmental change in normalized stereoacuity from age 2 years (Frisby) to age 4.5 years (Fly stereo test) between the hypoglycaemic and euglycaemic groups. Points at each age represent median values. Error bars represent the difference between the median values from 25th (below the median) and 75th (above the median) percentile. (N=190)

7.1.3. Effect of neonatal hypoglycaemia on the development of global motion perception

There was a non-significant trend towards a difference in the development of global motion perception between the hypoglycaemic and euglycaemic groups (Z= -1.83, *p*=0.06) whereby the hypoglycaemic group exhibited a slightly smaller improvement in motion coherence threshold from 2 to 4.5 years than the euglycaemic group (Figure 37). Exploration of this trend revealed that the normalized motion coherence thresholds were not significantly different between the two groups at either age (Mann-Whitney U test - at 2 years Z= -1.49, *p*=0.13; at 4.5 years Z= -1.38, *p*=0.16).

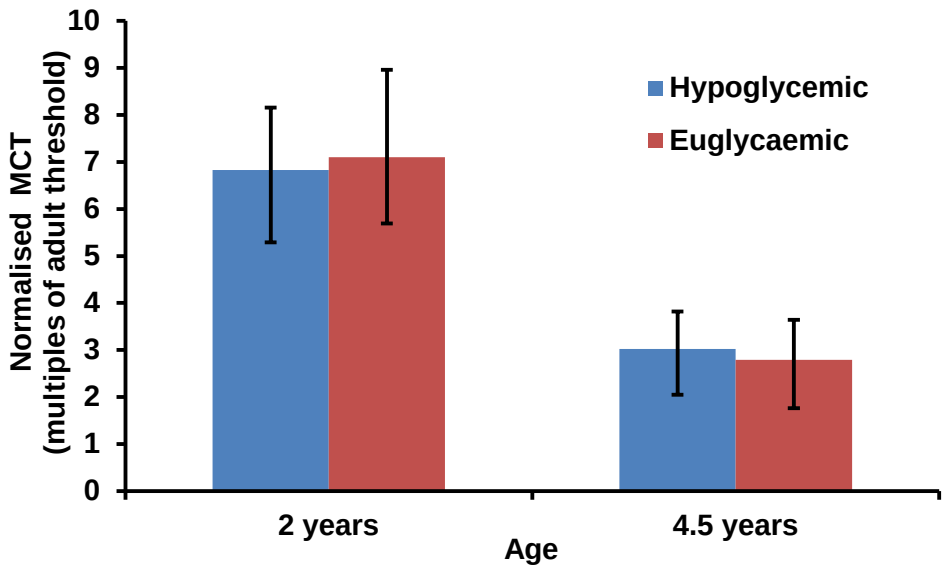

Figure 37. Median normalized motion coherence thresholds at 2 years and 4.5 for the hypoglycaemic and the euglycaemic groups. Error bars represent difference between the median values from the 25th (below the median) and the 75th (above the median) percentiles. (N=315)

7.2. Effect of individual risk factors on the development of visual function

There were no significant effects of hypoglycaemia on the development of visual acuity, stereopsis or global motion perception within the CHYLD study cohort. Hence, we were curious to explore whether the type or number of risk factors for neonatal hypoglycaemia influenced the development of visual functions. The different primary risk factors for neonatal hypoglycaemia present in the study cohort were: a) late preterm birth (N= 112), b) small for gestational age (SGA) (N= 53) c) large for gestational age (LGA) (N=35) d) infant of a diabetic mother (IDM) (N=144) and e) other (N= 11). Two of the risk factors (SGA and LGA) were mutually exclusive, whereas the others could have presented in combination, and babies could have more than one risk factor. Due to the potential for multiple risk factors, each baby was assigned a primary risk factor by team of experienced neonatologists. The procedure for assigning primary risk factors is described in Chapter 3 section 5.

7.2.1. Effect of risk factors for neonatal hypoglycaemia on the development of binocular visual acuity (BVA)

A Kruskal-Wallis H test revealed that there was no significant effect of primary risk factor group (preterm (N= 73), SGA (N=29), LGA (N=27), IDM (N=85) and other (N=9)) on the change in BVA from 2 to 4.5 years ($\chi^2(4) = 1.437$, $p = 0.838$). The median change for each group is shown in Figure 38.

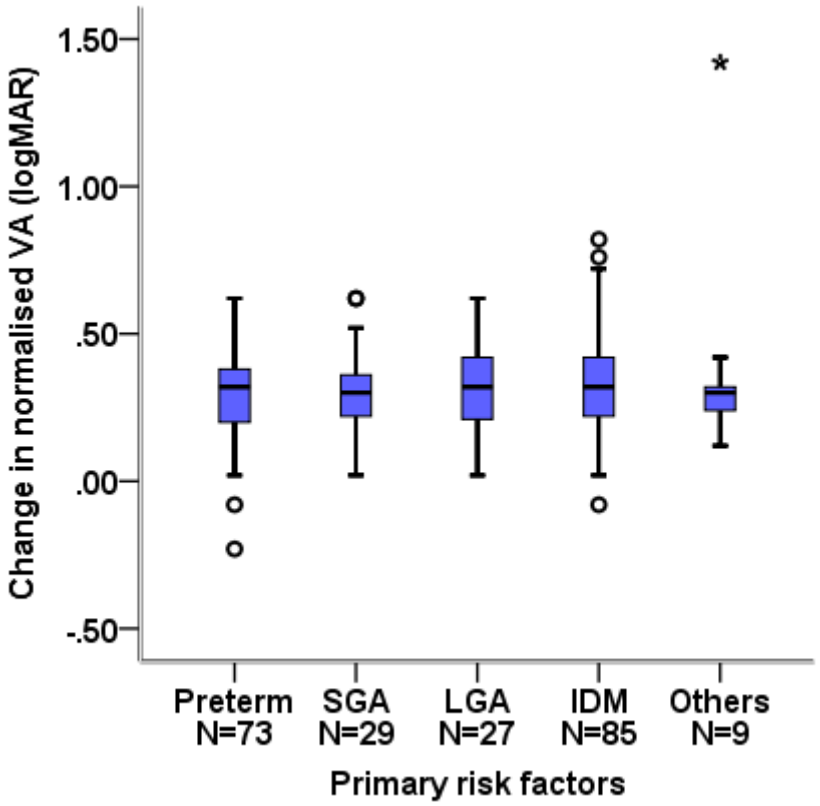

Figure 38. Developmental change in normalized binocular visual acuity for each primary risk factor group. Error bars and outliers are shown as in figure 21..

7.2.2 Effect of the risk factors for neonatal hypoglycaemia on the development of stereopsis

There was no difference in the development of stereoacuity between the risk factor groups (preterm (N=60), SGA (N=29), LGA (N= 23), IDDM (N=71) and others (N=7)) (Kruskal-Wallis H, χ^2 (4) = 2.789, *p*= 0.594). The changes in normalized stereoacuity (Frisby stereo test at 2 years and Fly stereo test at 4.5 years) for each of the risk factor groups are presented in Figure 39.

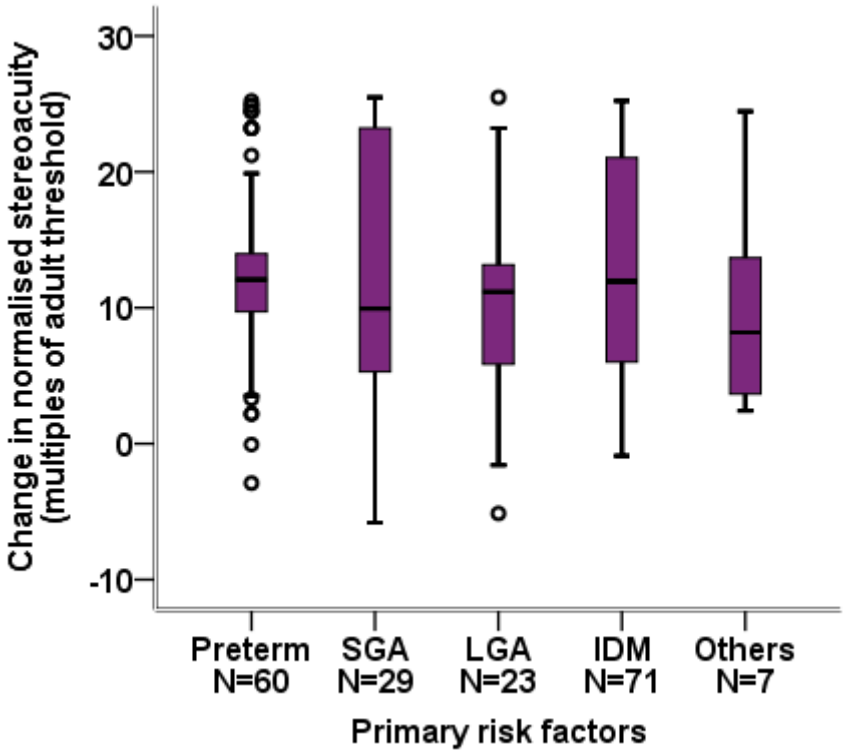

Figure 39. Developmental change in normalized stereoacuity for each primary risk factor group. Error bars and outliers are shown as in figure 21.

Similarly, there was no significant effect of risk factor group on the development of stereoacuity measured with the Lang stereo test at 2 years and the Fly stereo test at 4.5 years (Kruskal-Wallis χ^2(4) = 6.73, *p*=0.151).

7.2.3. Effect of risk factors on the development of global motion perception.

There was no significant effect of individual primary risk factor on the development of motion coherence thresholds from 2 to 4.5 years of age χ^2 =0.925, p=0.921 (Figure 40).

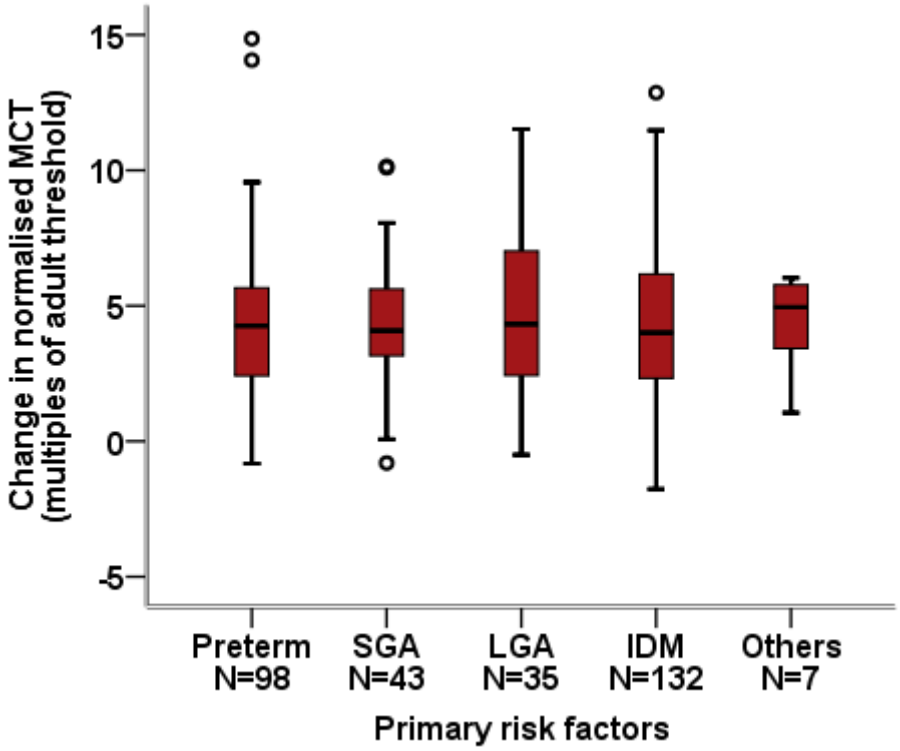

Figure 40. Developmental change in normalized MCT for each primary risk factor group**.** Error bars and outliers are shown as in figure 21.

7.3. Effects of multiple risk factors on the development of visual functions

An analysis of the effect of having a single risk factor or multiple risk factors for neonatal hypoglycaemia on the development of visual acuity, stereopsis and global motion perception was conducted. Children were categorized according to the number of risk factors present. Altogether, three categories were formed: children having one risk factor (N=150), two risk factors (N=193) and three risk factors (N=12).

7.3.1. Effects of multiple risk factors on the development of binocular visual acuity

Having multiple risk factors for neonatal hypoglycaemia did not significantly affect the development of BVA in our cohort (Kruskal-Wallis χ^2 (2) = 1.172, p=0.557). A further analysis was conducted which combined children having more than one risk factor into a multiple risk factors group. This was done because there were only 12 children with 3 risk factors. There was no significant difference in the development of BVA between the single and multiple risk factor groups (Z= -1.082, p=0.279).

7.3.2. Effect of multiple risk factors on the development of stereopsis

The change in stereoacuity from 2 to 4.5 years varied significantly across the number of risk factor groups when the Frisby stereo test was used at 2 years and the Fly stereo test was used at 4.5 years (Table 14). Children with three risk factors had the greatest change in stereopsis from 2 years to 4.5 years, followed by children having one risk factor and two risk factors. However, these findings need to be interpreted with caution as there were only five children in the three risk factors group. There was no significant effect of number of risk factors when the Lang stereo test was used at 2 years and the Fly stereo test was used at 4.5 years, χ^2 (2)= 3.485, p=0.175, N=278.

Table 14. Median change in normalized stereoacuity for children with one, two and three risk factors for neonatal hypoglycaemia.

Stereopsis tests	Median (IQR) change in normalized stereoacuity (multiples of adult threshold)			Significance
	One risk factor	**Two risk factors**	**Three risk factors**	
Frisby at 2 years vs. Stereo Fly at 4.5 years (N=190)	12.94 (6.02 to 21.04) (N=73)	11.30 (5.85 to 13.62) (N=112)	13.71 (12.57 to 24.83) (N=5)	$\chi^2(2)= 7.127$, p=0.028

Figure 41 illustrates normalized stereoacuity of children across three different risk factors at age 2 years and 4.5 years. It can be seen that the children within the three risk factors group improved more than the remaining two groups.

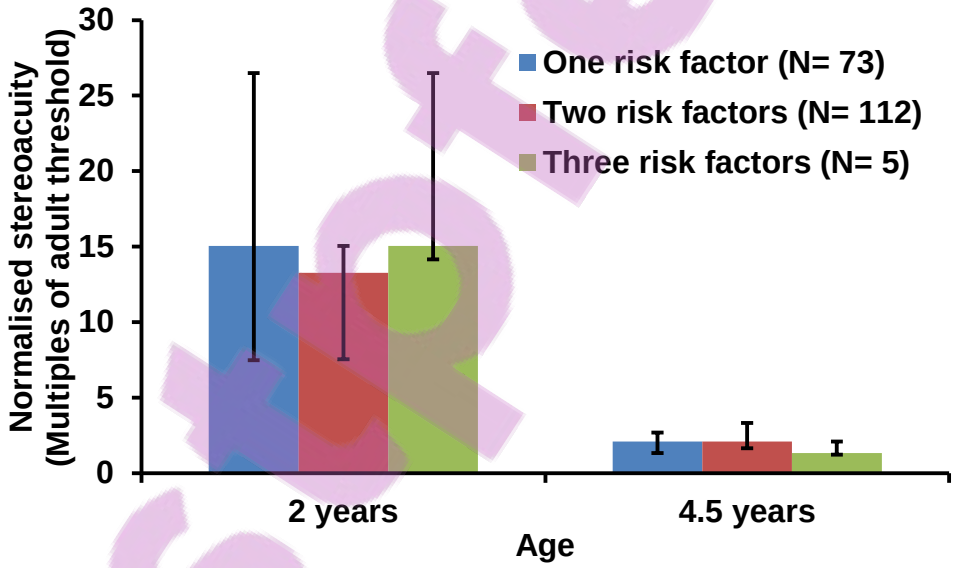

Figure 41. Change in normalized stereoacuity between three groups of risk factors. Error bars represent difference between the median values from 25th (below the median) and 75th (above the median) percentiles.

As the sample size in the three risk factors group was low, a further analysis was conducted between the single risk factor group and a multiple risk factor group that included children with two or three risk factors. The change in stereoacuity did not differ significantly between these two groups Z= -1.543, p=0.123 (Frisby versus Stereo fly), Z= -1.46, p=0.144 (Lang versus Fly stereo test).

7.3.3. Effect of multiple risk factors on the development of global motion perception

The development of global motion perception did not vary significantly as a function of the number of risk factors, although there was a non-significant trend towards children with a greater number of risk factors exhibiting a larger change in motion coherence thresholds from 2 to 4.5 years (χ^2 (2) = 5.943, *p*=0.051). A second analysis comparing the single risk factor group (N= 130) with a multiple risk factors group (N=185) that contained children with two and three risk factors revealed that children with multiple risk factors exhibited a significantly greater change in normalized measures of global motion perception than those with a single risk factor (Z= -2.481, *p*=0.013) (Figure 42).

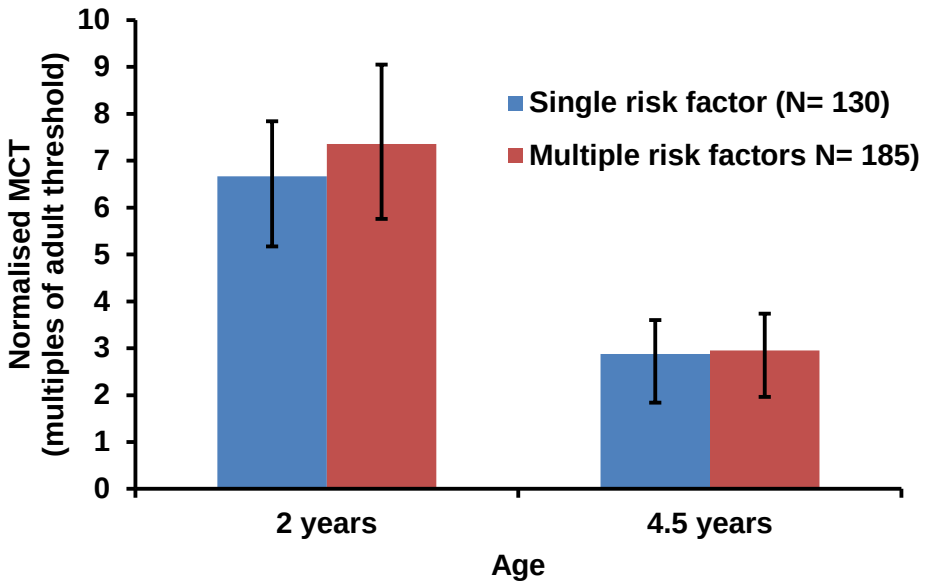

Figure 42. Change in normalized MCT between two groups of risk factors. Error bars represent difference between the median values from 25th (below the median) and 75th (above the median) percentiles.

The change in MCT performance between the single and multiple risk factor groups can be seen in Figure 39. It is evident that at 2 years, children with multiple risk factors had poorer performance than children with a single risk factor which was confirmed by Independent sample Mann Whitney U test (*p* = 0.008, Z= -2.667) . However, they caught up with the single risk factor children at age 4.5 years. (Mann Whitney U test, *p* = 0.22, Z= -1.22)

7.4. Summary on the effect of NH and its risk factors on the development of visual functions

The development of binocular visual acuity, stereopsis and global motion perception from age 2 years to age 4.5 years appeared not to be affected by hypoglycaemia or its risk factors. There was a trend for hypoglycaemic children to lag behind the euglycaemic children in terms of MCT development but this was not statistically significant. Furthermore, there was a statistically significant effect of single versus multiple risk factors on the development of global motion perception, but the size of this effect was very small (~1% coherence).

Chapter 8: Discussion

This chapter places the experimental results described in the preceding chapters in the context of the current literature. The chapter concludes by providing the limitations and strengths of the research described in this thesis.

8.1. Comparison of visual acuities measured using the Cardiff Acuity Cards, Lea Symbols and ETDRS chart in adults with normal vision

Chapter 5 explored agreements between acuity measurements obtained with adults, using the Cardiff Acuity Cards (CAC) and the Lea symbols (LS), which are the two tests used at different ages for the CHYLD study, and compared the findings with the gold standard ETDRS chart. To simulate refractive errors (which are common in children) (Breslin, O'Donoghue, & Saunders, 2013; Schimiti, Costa, Gregui, Kara-José, & Temporini, 2001) and visual impairment we also obtained results under different conditions of defocus. Those results showed that the CAC significantly overestimated visual acuity as compared to the LS and the ETDRS charts both under focused and defocused conditions.

The reason that adults were used for those comparisons was that we wanted to minimise the effects on the test results of cognitive factors. Visual function measurements obtained in children below 5 years can be highly variable (Mash et al., 1995) because their cognitive abilities have not yet reached adult levels and because the rate of development of the visual system varies between individuals. We recognise that cognitive factors play a major role in obtaining reliable measures of visual acuity and wanted to compare the different acuity tests to see if there were inherent differences not attributable to the cognitive demand of each test.

In this experiment we looked at the relationship between the charts using correlation and investigated the agreement between the tests by observing the 95% limits of agreement. There was a moderate and statistically significant correlation between the CAC and the LS under focused condition. This suggests that the values obtained with these two tests reasonably related with one another. The 95% limit of agreement between the CAC and the LS was ±0.20 logMAR which is within the range of the test retest reliability of commonly used visual acuity tests (± 0.10 to ± 0.30 logMAR) (Tonnie O. Adoh & Woodhouse, 1994; Tsirlin et al., 2015). This provided a justification for the use of the CAC and LS in determining visual functions in children. However, the mean difference of 0.30 logMAR between the tests under focused conditions and the proportional increase in bias with reduced acuity needed

to be accounted for in order to make fair comparisons. Hence, in the main CHYLD study, normalised acuity relative to adults was used for assessing development from 2 years to 4.5 years. The increase in the mean difference between the CAC and LS with increasing defocus indicates that the results could be different in the presence of refractive errors. This could have influenced the comparison of 2 years and 4.5 years visual acuity data. This is discussed in chapter 5 section 5.

With regard to the LS and ETDRS chart comparison, the limits of agreement were ± 0.15 logMAR which is within the acceptable range of test retest reliability for gold standard adult acuity charts (Tsirlin et al., 2015). Furthermore, there was a non-significant mean difference between these two tests. This suggests that measurements made using these two tests were in good agreement with one another. The measures of the CAC and those of the ETDRS, however, were not significantly correlated with one another but the limits of agreement were similar to that between the CAC and the LS (±0.30 logMAR). The CAC overestimated VA also by 0.30 logMAR in comparison to ETDRS.

It was also demonstrated in the experiment that spherical defocus has a different impact to astigmatic defocus on different paediatric acuity charts. The results are consistent with a study by Little et al., (2012) in which a range of astigmatic defocus levels had differing effects on commonly used paediatric visual acuity charts. However, a direct comparison of that study with our study was not possible because the charts used in the Little et al. study were not the same. Little et al., (2012) used Keeler crowded logMAR, single letter acuity test, the single letter Sheridan Gardiner chart, the crowded and single Kay picture tests. In our experiment the CAC was the most resistant and the ETDRS chart was the most susceptible visual acuity test to both the spherical and the astigmatic defocus. This indicated that CAC could be less able to detect astigmatic and spherical blur. This might have direct clinical implications in terms of detecting poor visual acuity in children due to refractive errors. One study (Howard & Firth, 2006) compared the ability of the CAC with that of the Bailey-Lovie LogMAR chart in detecting reduced vision as a result of refractive errors in children. Howard and Frith showed that the CAC was less sensitive than the Bailey-Lovie logMAR chart in picking up reduced visual acuity due to refractive errors in children whereby only 25% of visual acuity reduction due to refractive errors was detected by the CAC as compared to 97% detection by the Bailey-Lovie logMAR chart. The LS and the ETDRS charts were equally susceptible to both spherical and astigmatic blur which suggests that they are comparable for use in detecting reduced visual acuity due to refractive error. However, it should be noted that these tests of acuity cannot be implemented in 2 year-old children. The youngest children that have performed LS acuity test, as recorded in the literature are 2.5 years of age (Becker & Hübsch, 2002).

Taken together, our observations in adults suggest that the CAC and LS test results are reasonably related to one another in the absence of cognitive influence. Our findings show that the CAC over-estimates visual performance and we propose that an offset of visual acuity (equivalent to the mean difference between the charts) needs to be accounted for to equate measures made using the CAC with those made using the LS. As we were interested in the longitudinal development of visual acuity in the overall project, the use of the CAC at age 2 years and the LS at age 4.5 years was justified by looking at the reasonable limits of agreement and the moderate relationship between these two tests. Nevertheless, the CAC overestimated VA over the LS more with increasing levels of poor visual acuity (proportional bias). This made us difficult to determine a single correction factor. This was one of the main reasons for normalising the children's data in this study.

8.2 The development visual acuity, stereopsis and global motion perception from 2 to 4.5 years of age

8.2.1. Normalization of the measures

We used different age appropriate clinical and psychophysical tests to observe the developmental change in visual performance from 2 years to 4.5 years of age. Age appropriate tests were chosen over the use of the same test at both ages because the use of age appropriate tests minimizes the impact of cognitive development on test performance. This is because age appropriate tests are designed for the cognitive ability of the target age group. The disadvantage of this approach was that the raw results of each test at each age could not be directly compared due to differences in test and stimulus design. To solve this issue we normalized the children's data to adult median values that we obtained empirically for each test. There are some methods reported in the literature on utilizing adult thresholds for visual development studies such as visualising the development of visual functions at different ages or determining an age at which children's performance reaches half the adult performance. Teller in her paper on the development of various visual functions in infancy plotted a graph which she called a Palmer's plot, which according to her was based on a personal communication with one of her colleagues John Palmer.(Teller, 1997) The plot depicts the maturation rate of various visual functions relative to the adult level. Similarly, Carkeet et al have utilised adult thresholds in order to determine the age at which children attain half of the adult performance for vernier acuity and resolution acuity. (Carkeet et al., 1997) Their method was based on least squares regression. While these studies have utilised adult thresholds to observe the development of visual functions, the same test was used at different ages. To the best of my knowledge, the work presented in this thesis is the

first to utilise adult thresholds in order to study the longitudinal development of visual functions using different tests at different ages. The process of normalisation described in this thesis was inspired by the Teller's paper on infant visual maturation.

8.2.2. Prevalence of eye and vision disorders at age 2 years and at age 4.5 years

It was interesting to note that there was a higher prevalence of eye and vision disorders at 4.5 years than at 2 years. Most of the visual disorders were related to abnormal visual acuity findings at 4.5 years and abnormal visual acuity and refractive error at 2 years. In particular, the visual disorders more prevalent at 4.5 years were reduced habitual visual acuity and strabismus. There are several possible explanations for this result. One possible explanation could be the poor sensitivity of the CAC in detecting reduced visual acuity which was confirmed by our study (Chapter 5) and one other previous study (Howard & Firth, 2006). Therefore poor VA could have been undetected at 2 years but detected at 4.5 years. Another possible explanation lies in the measurement of visual acuity whereby binocular visual acuity was measured at 2 years and both monocular and binocular VA was measured at 4.5 years. At 2 years visual acuity assessment only detected visual defects that were present in the better eye. Monocular conditions such as monocular amblyopia would have been missed. However, as automated refraction was conducted at 2 years, it is unlikely that children with refractive amblyopia were missed. A further explanation of this finding could be the fact that at 4.5 years of age we considered children who were uncooperative for use of any acuity test (11 uncooperative for visual acuity testing out of 42 considered as abnormal) as children having abnormal vision which might not have always been the case. Nevertheless, even after excluding the children who were un-cooperative, the prevalence of children who had abnormal visual acuity was considerably higher at 4.5 years - 1.7% at 2 years versus 8.7 % at 4.5 years. Therefore, from our study it was observed that children may develop reduced visual acuity later in life; even if they appear to have normal visual acuity at a younger age. However, the fact that the criteria for considering abnormal visual acuity at age 2 years might have been relatively too loose must also be acknowledged with regards to this finding.

By comparison, the prevalence of strabismus was higher at 2 years than at 4.5 years. This finding suggests that manifest strabismus could be detected early in childhood. However, an interesting observation in the strabismus findings was the development of normal binocular vision at 4.5 years in four out of nine children who were diagnosed as having strabismus at 2 years. All of the four children achieving normal binocularity had esotropia (two had right esotropia and two had alternating esotropia) at 2 years. We referred these children to an

appropriate eye care provider, which means the children might have received appropriate refractive correction, which aligned their eyes if they had accommodative component involved in the deviation. As we were unable to obtain the records of the children whom we referred, therefore these possibilities cannot be confirmed.

We observed that children who we assessed as having abnormal binocular acuity at 2 years with the CAC, developed acuity within normal range at age 4.5 years when tested with the LS. This suggests that abnormal visual acuities obtained at younger age by CAC do not necessarily mean that the child will have abnormal visual development in the long run. It should be acknowledged that only a small number of children were outside the normal range at 2 years. However, it can be inferred that acuity measures at 2 years may not predict the long-term visual outcome. When we examined the status of visual acuity at 2 years those children who were abnormal at 4.5 years, we found that the majority of children were normal at 2 years. Moreover, we did not detect any ophthalmic abnormalities in these same children at 2 years.

Overall these findings suggest that visual status at an early age do not necessarily predict visual status at an older age.

8.2.3. Developmental change of visual acuity from 2 to 4.5 years of age

It is well known that there is rapid development of visual acuity during the first year of life. Binocular visual acuity (BVA) as measured with the TAC changes from 1 cycle per degree at birth to 6-10 cycles per degree at 1 year of age (Teller & McDonald, 1986). After this, there appears to be a slow developmental phase up until 5 – 10 years of age depending upon the component of the visual acuity being measured. As discussed in the development of visual function section of Chapter 2, each of the visual acuity components has their own maturation period. Visual development is generally assessed using the same test at all measurement points from birth until maturation (Beiser et al., 1995; Mayer & Dobson, 1982). However, in our study, we did not follow this procedure but instead have used age appropriate tests to determine the development of visual function relative to adult level. To avoid the problems generated by using the absolute raw values found at the 2 different ages, (where any development of visual function was not evident) we used the normalised values which illustrate that there is a clear picture of a considerable improvement in visual acuity performance from 2 to 4.5 years of age. There was a change of almost one octave (0.26 logMAR, or 1.8x improvement) in acuity performance from 2 to 4.5 years of age. This value

is similar to the change in monocular grating acuity from 2 to 4 years of age (0.30 logMAR) – 10 cycles / degree at 2 years to 25 cycles / degree at 4.5 years found by Mayer et al (Mayer, Beiser, Raye, & Lang, 1995). Consistent with other findings (Leat et al., 2009), the children in our cohort had not attained an adult level of recognition visual acuity (-0.16 logMAR) at 4.5 years which supports the conclusion that recognition acuity continues to develop past 4.5 years of age.

It is interesting that there was a considerable improvement in visual acuity from 2 to 4.5 years for those children who had poor visual acuity at 2 years. This finding is in accordance with a study by Saunders at al. (Saunders, Westall, & Woodhouse, 1996) where they demonstrated that while children whose findings are normal at a young age tend to maintain a smooth trend of development, those who were diagnosed as abnormal have a highly unpredictable pattern of development. They reported that most of the children with abnormal visual acuity at baseline had a variable development pattern but eventually attained above average acuity at 3 years as measured with the Teller Acuity Cards. These results may reflect a “catch up” in visual acuity during the preschool years for children with poor VA in infancy, a change in the ability of children to comply with vision testing or both. However, there is some possibility that this change could be an artefact as there is a chance that extreme values that arise by random variation tend to regress to the mean on a second measurement.(Barnett, van der Pols, Dobson, Pols, & Dobson, 2005; Bland & Altman, 1994) Measures of test-retest variability using the same test would have addressed this issue; however this was not possible in the current study due to the extensive testing that CHYLD study participants completed during their assessment visit.

8.2.4. Developmental change of stereopsis from 2 to 4.5 years of age

The considerable development of stereopsis from 2 years to 4.5 years is evident from both the raw and normalised measures (Figures 3 and 4). The median raw developmental change in stereopsis using the Frisby test at 2 years and the Fly stereo test at 4.5 years was 237 seconds of arc whereas the normalised change was by a factor of 11.5. Most of the children didn’t attain adult threshold at 4.5 years which suggests that stereopsis continues to develop after 4.5 years. This is in accordance with previous published studies (Ciner, 1991; Ciner, 1996). Our median raw stereopsis of 300 seconds of arc (mean- 332 seconds of arc) with the Frisby stereo test in 2 year old children was slightly poorer than that obtained by Ciner (1991) in a group of normal children 24-29 months of age (mean, 250 seconds of arc) using FPL random dot stereo targets. However, our raw stereoacuity median finding of 63 seconds

of arc (mean, 86 seconds of arc) at 4.5 years was better than the mean stereoacuity of 100 seconds of arc of 48-53 months children in the Ciner study. The study of Ciner and the work reported in this thesis used stereopsis scores normalised to adult levels for comparison purposes. Comparing the normalised measures, stereoacuity at 2 years in our cohort was worse by a median factor of 13 times relative to adults (mean: 15) as compared to a mean worse performance by a factor of 11.25 X in Ciner study. However, at 4.5 years, children were worse than adults by just a factor of 2 in our study compared to a mean worse performance of a factor of 5 in the Ciner study. Nevertheless, this study could have overestimated the stereoacuity of the children at 4.5 years as the minimum threshold that could be measured with the Fly stereo test was 20 seconds of arc and it is likely that some adults could have easily gone below this threshold level.

Ciner and colleagues (Ciner et al., 1996) later developed a new stereopsis test with a happy face target and incorporated the FPL method and found mean stereoacuity of 101.7 seconds of arc in children of 24-29 months and 48 seconds of arc in children of 48-53 month olds. The raw stereopsis findings with the new test at both of the ages were better than our findings. Birch et al (Birch et al., 2008) used the Randot Preschool Stereoacuity test in a large cohort of 3 – 18 year old children and found a median stereoacuity of 300 seconds of arc in 3-year-old children and 111 seconds of arc in 4-year-old children. The disparity limit presented by the test (a threshold of 20 seconds of arc) was obtained by 47% of the children aged 11-18 years. This further indicates that stereopsis continues to develop at least until 18 years of age. A number of factors may account for these mixed findings. Firstly, none of the described studies have used the same stimulus; exact comparison, therefore, is not possible. Secondly, stereopsis was measured in normal children in other studies whereas all our study children were born at risk of neonatal hypoglycaemia. Therefore we might expect poorer thresholds if development in our cohort had been influenced by the presence of any risk factor for neonatal hypoglycaemia. This will be discussed in section 8.4. Nevertheless, the majority of studies including ours, no matter what stimuli have been used, agree that stereopsis continues to mature after 4.5 years. However a small number of studies have shown that stereopsis matures earlier that 4.5 years (Fox et al., 1986) or even at 6 months (Birch & Petrig, 1996).

The raw measures of the Lang stereo test at 2 years and the Fly stereo test at 4.5 years also showed that there was considerable improvement in stereoacuity over the intervening period of 2.5 years (median improvement of 337 seconds of arc). However, a normalised comparison showed that the stereoacuity threshold was reduced at 4.5 years. This was because we were not able to obtain adult thresholds due to the ceiling effect in the Lang stereo test where the maximum measurable stereopsis was limited to 200 seconds of arc.

In broad terms, given the diverse range of tests used in this area, the development of stereoacuity from 2 to 4.5 years appears to be fairly equivalent among studies and the stereopsis values that we obtained in our cohort did not deviate that far from the normal population (Simons, 1981). The difference in absolute values observed, however, seems to be due to the use of different tests.

8.2.5. Developmental change of global motion perception from 2 years to 4.5 years of age

This was the first study to explore the development of global motion perception in children from 2 to 4.5 years of age. The lack of such studies in the literature could be due to the inherent difficulty in determining visual function using psychophysical tests in children of this age group. Our findings suggest that there is a considerable improvement in global motion perception performance where the median change in normalized performance was by a factor of 4. We could not compare the developmental change in our study with that of previous studies because none exist that have longitudinally assessed global motion perception from 2 years to 4.5 years. However, our global motion perception findings at 4.5 years showed that global motion function was not mature until at this age. This is in line with previous studies (Ellemberg, Lewis, Maurer, Brar, & Brent, 2002; Gunn et al., 2002; Hadad, Maurer, & Lewis, 2011; Narasimhan & Giaschi, 2012; Parrish, Giaschi, Boden, & Dougherty, 2005).

Even though our study was consistent in showing that global motion perception is not mature at 4.5 years of age, the actual threshold of 4.5 years old children in our study was worse by a factor of 3 compared to adult thresholds. This is in contrast with other studies where the difference between thresholds of 4 to 5 year old normal children or hemiplegic children and adults is a factor of less than 2 (Gunn et al., 2002; Parrish et al., 2005). This discrepancy most probably lies in the design of the methods used to obtain thresholds. Gunn et al used a segregated global motion task with stimulus presentation for a longer duration (maximum of 10s) than ours (Gunn et al., 2002) while we used a translational global motion task with a stimulus duration of 1s. Dot density in our motion coherence task was 1.27 dots/degree^2 unlike 4 dots/degree^2 in their study. Similarly, Parrish et al., (2005) used dot density of 32 dots/degree^2 with the dot speed of 1.2 degrees/sec unlike the dot speed of 6 degrees/sec in our study. Moreover, the stimulus duration was 854ms in their study. Narasimhan & Giaschi (2012) demonstrated that global motion perception matures earlier when a faster speed (4 degrees/second) is used with a high dot density (30dots/degree^2) which explains the

difference in the discrepancy between our study and other studies. Our stimulus had lower dot density than the stimulus used in both of these studies but had faster speed than the Parrish et al.,(2005) study.

To summarise, our findings suggest that there is a marked improvement of global motion perception from 2 years to 4.5 years. This improvement indicates that the duration between 2 years to 4.5 years is a period when a considerable proportion of the global motion perception development occurs.

8.2.6. Summary of the development of binocular visual acuity, stereopsis and global motion perception from 2 to 4.5 years

Among the three visual functions we assessed, maximum improvement was observed for stereoacuity, where there was a change by a factor of 13. The changes in global motion perception (4X) and visual acuity (2X) were less marked but still large. This indicates there was a substantial development in visual processing from 2- 4.5 years. This change could be the actual development in performance or could be due to the development of attention and cognitive from 2 to 4.5 years which contributes to the improved compliance of children to obtain threshold measures. It is worth noting that factors relating to compliance and attention were controlled as much as possible by the use of age appropriate tests in this study, which means that the changes in these functions are likely to reflect actual changes in these functions from 2 to 4.5 years of age.

8.2.7. Relationship between the measures of binocular visual acuity, stereopsis and global motion perception at 2 years and 4.5 years using age appropriate tests

There was a weak but statistically significant relationship between CAC acuity at 2 years and LS acuity at 4.5 years. These findings indicate that measures of acuity at 2 years only partially predict visual outcome at 4.5 years. The reason for this weak relationship seems most likely to be due to the range of acuities that we have in our cohort. In order to observe a good correlation, there needs to be wide spread of data; however, our spread of data for visual acuity was relatively small (more than 95% of the children had acuity within normal range). This assumption was further supported by an observation of a slightly stronger correlation between the same two tests in a subset of 4.5 year old children where the visual acuity data was more variable (Figure 33).

Our finding that acuity measures at a young age do not strongly predict long-term visual outcomes, especially for children who have abnormal visual acuities, have been reported by other studies (Dobson et al., 1999; Hall, Courage, & Adams, 2000) . Dobson et al explored the relationship between grating acuity (Teller acuity cards, TAC) at 1 year of age and Snellen acuity at 5.5 years in preterm children. Their study group contained a bimodal distribution of acuities where children were either legally blind or had vision within the normal range. Those studies showed that the majority of children who were had normal grating acuities in infancy remained within normal levels for Snellen letter acuity at 5.5 years and children who were detected as being legally blind during infancy still remained at this level at 5.5 years. However, there were 4 eyes that were considered within normal range with the TAC at 1 year but that had equal to or worse than 6/60 Snellen letter acuity at 5.5 years and 11 eyes that were considered normal at 1 year with the TAC and were found to be abnormal at 5.5 years again with the TAC. In a case-by-case evaluation of these children these authors found that all of the children who were normal at 1 year and abnormal at 5.5 years had one or more than one ocular abnormality such as nystagmus, strabismus, high myopia and macular disorders. This was unlike our study where we were unable to find any obvious ocular pathology at 2 years of age in children who were abnormal at 4.5 years of age. O'Connor et al (O'Connor, Spencer, & Birch, 2007) in a population of extremely low birth weight children provided further evidence that the TAC results in infancy do not reliably predict long term visual outcomes. Further support that even use of the same test or different tests at 2 points of time may not predict long term acuity has been demonstrated by Hall, Courage and Adams (Hall et al., 2000) where the TAC acuity measured early in life was not correlated with measures of the TAC acuity (r=0.04) or recognition acuity (r=0.08) measures after 5 years of age.

Conversely, Mash and Dobson (Mash & Dobson, 1998) completed a longitudinal follow-up study of preterm children across the ages of 4 months to 4 years. They compared Teller Acuity Card (TAC) values at 4, 8, 11, 17, 24 and 36 months with the TAC and acuity measures made with the HOTV chart at 4 years. The correlations between the TAC at younger ages and TAC at 4 years ranged from 0.13 to 0.59. The correlations between the TAC at younger ages and the HOTV letter chart at 4 years ranged from 0.22 to 0.61. All of the correlations were statistically significant. Even though their correlation coefficients between acuity tests and ours can't be directly compared due to the difference in the tests used at different ages, the correlation between their TAC acuity measures at 2 years and recognition acuity at 4 years was of a similar magnitude (r= 0.31, p <0.01) to ours (rho = 0.20, p= 0.003).

Our study is the first study that looked at the relationship between CAC at 2 years and LS acuity at 4.5 years. Consistent with other longitudinal studies (Hall et al., 2000; Mash & Dobson, 1998; O'Connor et al., 2007) there does not seem to be a high agreement between values obtained with tests measured at a young age and those obtained at an older age. This appears to be true when either the same test is used or when different tests are use at different ages. This finding that there is only poor agreement between measurements at different ages could be due to the inherent variability of visual acuity measurements made at each age (repeatability has been shown to be ±0.30 logMAR) (Anstice & Thompson, 2014; Tsirlin et al., 2015).

There was no correlation between the results of the Frisby stereo test (used at 2 years) and those of the Fly stereo test (used at 4.5 years) in our cohort. It is hard to explain this finding but one possibility could be the use of two different mechanisms to produce the retinal disparities that are the basis of stereo depth perception in each of these tests. The Frisby stereo test uses objects in real depth whereas the Stereo fly stereo test uses to images presented to separate eyes using the vectographic polarisation principle (Leske et al., 2006). The other difference between the tests is that the Frisby test presents stimuli comprised of random elements and is likely to require higher cortical functions to perceive the circular targets at different depths. The significant correlation between the Lang (at 2 years) and the Fly stereo test (at 4.5 years) we observed may not represent a real correlation between the two tests because of the inherent design of the Lang test that limited thresholds to 200 seconds of arc at best.

The absence of a relationship between global motion perception measures at 2 years and 4.5 years was contrary to our expectations. OKN eye movements are likely to be governed by sub-cortical neurons (neurons of the nucleus of the optic tract) until a few weeks after birth and gradually rely on cortical processing with a full transition to cortical processing at the age of 3 to 6 months. (Atkinson, 1979) However, there is some evidence that subcortical areas still provide partial input to the OKN eye movements at least up to 2 years of age (Lewis, Maurer, & Chung, 2000). Hence there is a possibility that different pathways could have been involved in perceiving global motion at 2 years and 4.5 years. However, this explanation for the lack of a relationship between the global motion measures made at 2 and 4.5 years of age is unlikely. In adults there was a strong correlation (intra class correlation - 0.81) between OKN-based and behavioural measures of global motion perception suggesting that the two measures assess a common motion processing mechanism (Yu et al., 2013).

Another possible explanation for the lack of a relationship between global motion measures made at 2 and 45 years of age is that the stimulus properties used for testing at 2 years and 4.5 years of age were different. As mentioned in sections 1.1.3 and 2.1.3 of Chapter 4, the 2 year old protocol was optimised for OKN eye movements which required larger dots (0.5 degrees), an optimal speed (8 degrees/second), an appropriate stimulus duration (8 seconds) and dot density (1.16 dots/degree^2) whereas for 4.5 years the dot size was smaller (0.24 degrees), speed was slightly slower (6 degrees per second) duration was shorter (1000ms) and dots were slightly more dense (1.27 dots / degree^2) in order to be consistent with the previous literature.(Lewis & Maurer, 2005; Narasimhan & Giaschi, 2012) As suggested by Narasimhan & Giaschi (2012) the maturation of global motion perception depends upon dot speed and dot density which could have influenced our results. Even so the use of different parameters at two ages doesn't solely explain the lack of relationship. This is because, the parameters of the motion coherence test stimuli used for different age groups our study were not sufficient to result in a large difference in the threshold. Narasimhan and Giashi (2012) tested children under three different dot density conditions (1 dot/deg^2, 15 dots/deg^2 and 30 dots/deg^2) and 2 different speeds (1 deg/sec and 4 deg /sec). Compared to their study, the difference in the dot density between the stimuli used in 2 ages in our study was negligible (difference of 0.11 dots/deg^2) and the difference in the dot speed was 2 deg / sec and hence it is unclear if this difference in dot density and speed would influence the obtained threshold.

Furthermore, the lack of relationship between measures of global motion perception at 2 years and 4.5 years could be due to the use of different methods to estimate threshold at different ages. Method of constant stimuli was used at 2 years whereas a proportional staircase method was used at 4.5 years. However, as mentioned in sections 4.1.1.3 and 4.2.1.3, the use of method of constant stimuli was inevitable at 2 years because the judgement of eye movements in real time was impossible when staircase method was used. Similarly, the use of constant stimuli was not possible in 4.5 year old children because the stimulus was unable to hold enough attention to obtain a reliable threshold.

The duration of the stimulus in the test used at 2 years was 8 seconds, which could have provided different thresholds than the 1-second presentation used at 4.5 years of age. Previous studies have found that with increasing stimulus duration there is an increase in global motion perception performance but only up to a limit of 900ms (Downing & Movshon, 1989). If this is the case then presentation time may not have had a large effect on thresholds as both of our stimuli were presented for longer than 900ms. Some previous studies also have shown that stimulus area affects motion coherence thresholds but reaches an asymptote level after 25 deg^2 (Downing & Movshon, 1989). The stimulus areas we used

for both the 2 years and 4.5 years tests were higher than the asymptote level and therefore stimulus area may not have affected threshold in this study.

Although global motion stimulus differences complicated the comparison of the 2 and 4.5 year datasets, these differences were mostly unavoidable. This is because the task for 2 year old children was designed to optimise cross sectional measurements of global motion perception using OKN eye movements and the task for the 4.5 year old children was designed to improve cross sectional testability for a behavioural psychophysical test.

8.3. The effect of neonatal hypoglycaemia and its risk factors on the development of visual acuity, stereopsis and global motion perception

Our cohort of children was representative of the overall cohort of the CHYLD study (McKinlay et al., 2015) even though only those children who were successfully followed up at both 2 years and 4.5 years were included in this study. Fifty four percent of the children in our cohort had experienced short episodes of hypoglycaemia as compared to 53% of the children in the whole cohort.

Our study did not find an effect of neonatal hypoglycaemia on the development of visual acuity, stereopsis and global motion perception between the ages of 2 and 4.5 years. Possible explanations for these findings will be discussed in the following sections.

8.3.1. The effect of NH on the development of binocular visual acuity

The development of binocular visual acuity from 2 to 4.5 years of age was not significantly different between the hypoglycaemic and euglycaemic children. The median difference in normalised change in binocular visual acuity between hypoglycaemic and non-hypoglycaemic group was 0.02 LogMAR. This difference is only one letter (1/5th of a line on a standard chart).

There are several possible explanations for this result. The most convincing explanation would be the fact that the hypoglycaemic children received appropriate treatment as soon as they were detected. Another possible explanation is that any visual acuity deficit at birth had been reversed with the development of visual acuity by the time they reached 2 years and that development was the same as that experienced by the non-hypoglycaemic group thereafter. It is also possible that the children who experienced neonatal hypoglycaemia may yet have abnormal development after 4.5 years. Some studies have shown that children born with various perinatal risk factors may show abnormal acuity until up to 10 years of age

or even adulthood (Cooke, 2004; Kok et al., 2007). Some authors assert that to understand the long term effect of prenatal adversity on visual acuity, VA needs to be assessed after 6 years, as tests used before this age are not robust enough to detect subtle defects (O'Connor & Fielder, 2007).

8.3.2. The effect of NH on the development of stereopsis

There was no association between hypoglycaemia at birth and stereopsis development from 2 to 4.5 years of age. This is also probably due to the successful early treatment of hypoglycaemia. . Another possibility could be the fact that clinical tests of stereopsis may not be able to detect subtle changes in stereopsis development (Ferrer-Blasco, Madrid-Costa, García-Lázaro, Cerviño, & Montés-Micó, 2011; Leske et al., 2006). This is because these tests suffer from a number disadvantages such as: fewer trials at each level of disparity, unsystematic estimation of threshold and large step size (Bach, Schmitt, Kromeier, & Kommerell, 2001).

8.3.3. The effect of NH of the development of global motion perception

There was no significant influence of hypoglycaemia on the development of global motion perception. The most likely reason again could be the fact that the hypoglycaemic children were provided immediate treatment. Previous studies (Alkalay et al., 2005; Filan et al., 2006; Tam et al., 2008) have found that severe hypoglycaemia is associated with visual disorders but the effect of mild to moderate hypoglycaemia was unknown. This study provides good evidence that trying to maintain blood glucose level >2.6 mmol/L (Cornblath et al., 2000), which is a current common practice among clinicians, allows for normal visual development until at least 4.5 years of age.

8.3.4. Summary of the effect of NH on the development of visual acuity, stereopsis and global motion perception

Our study did not demonstrate a link between neonatal experience of hypoglycaemia and the development of binocular visual acuity, stereopsis and global motion perception. The possible explanation lies in the effective treatment of the hypoglycaemic children. Furthermore, as already stated, our study considered blood glucose level of <2.6 mmol/L

during the first 48 hours of birth as neonatal hypoglycaemia, which is the currently widely accepted clinical guideline for the care of neonates (Cornblath et al., 2000). However, previous studies that have shown abnormal visual development have used blood glucose criteria that were lower than ours, or, had only patients who had a blood glucose level of <2.1 mmol/L (Murakami et al., 1999; E. W. Y. Tam et al., 2008). For instance, Murakami et al.,(1999) in their 8 patient case series observed abnormal visual development (strabismus, impaired visual acuity, and nystagmus) in 50% of their cases. However, all of the children in their study had blood glucose levels of <1.1mmol/L. Similarly, Tam et al.,(2008) showed cortical blindness in 2 out of 18 patients examined and found abnormal VEPs in 11 out of 20 infants. However, they also included children whose blood glucose level was only <2.1 mmol/L. These findings may indicate that the blood glucose level of 2.6 mmol/L, which is currently used as a criterion to determine cut-off for neonatal hypoglycaemia, is safe with regard to visual development.

Another possible reason that visual functions developed normally for the children our study could be that NH did damage the visual pathways but that this was reversed by the plasticity of the developing brain. Several studies in the field of neonatal hypoglycaemia research support this hypothesis (Filan et al., 2006; Kinnala et al., 1999). Filan et al., (2006) in their case series involving 4 infants found that even though all of the four infants had extensive lesions located in the occipital region of the brain as demonstrated by MRI only one child developed abnormal visual development in the long term. Similarly, Kinnala et al., (1999) demonstrated that out of the 18 hypoglycaemic children, 7 had brain injuries (as detected via MRI and ultrasonography) but only one showed abnormal neurodevelopment, which suggests that these lesions have a tendency to recover functionally. Other studies have also shown relatively normal performance of children later in their life after extensive occipital lobe injury in infancy (M.G.Knyazeva, P.Maeder, D.C.Kiper, T.Deonna, & G.M.Innocenti, 2002). There is significant evidence in the literature supporting reorganization of the brain after early brain injury (Andrea Guzzetta et al., 2010).

As our study ended when the study cohort reached 4.5 years, it is possible that these children may develop global motion perception deficits later in life as it has been observed with other developmental disorders (Atkinson & Anker, 2001; Atkinson et al., 1997; Kogan et al., 2004; Pellicano et al., 2005; Slaghuis & Ryan, 1999; Spencer et al., 2000; Talcott et al., 2000). This is because global motion perception continues to develop into late childhood (Gunn et al., 2002; Hadad, Maurer, & Lewis, 2011).

Taken together, proper and early treatment of hypoglycaemia appears to be the most convincing explanation for the demonstration of normal development of visual acuity,

stereopsis and global motion perception of hypoglycaemic children in our study. However, there is a possibility that visual deficits may develop later in life in children with a history of hypoglycaemia.

8.4. The effect of risk factors for NH on the development of visual acuity, stereopsis and global motion perception

An exploration of the effect of risk factors for neonatal hypoglycaemia on the development of visual functions did not demonstrate an influence of individual primary risk factors on the development of binocular visual acuity, stereopsis and global motion perception from 2 to 4.5 years of age. There was a significant effect of multiple risk factors on the development of global motion perception where children with multiple risk factors had significantly greater developmental change. This finding was surprising because children with three risk factors were found to have severe (<2.00 mmol/L) hypoglycaemia (Harris, Weston, & Harding, 2012). It would be expected that children with hypoglycaemia would lag behind in their development, but it was seen that these children were slightly poorer at two years whereas they caught up with the single risk factor group within a period of 2.5 years. The risk factors for the children included in this study were- late preterm (35-37 weeks of gestation), born to diabetic mothers, small for gestational age, large for gestational age and others (congenital abnormalities). Even though there is literature suggesting preterm birth affects visual development (visual acuity, global motion perception) (Birch & O'Connor, 2001; Guzzetta et al., 2009; Santos, Duret, Mancini, Gire, & Deruelle, 2009), our study was did not demonstrate that preterm birth effected visual development more than any other risk factors for neonatal hypoglycaemia. As all of the children involved in the CHYLD study were born with risk factors for NH, a comparison with children having no risk factors was not possible. Previous studies (Getz, Dobson, & Luna, 1994) have also shown that small for gestational age children may have abnormal visual development, when compared to children who were born appropriate for gestational age, only when recognition tasks are implemented. A comparison with children who were completely normal was not possible in our study; however the results do not suggest that being born small for gestational age affects visual development more than any of the other risk factors present in the study cohort.

Future research comparing visual development in children born with risk factors for NH with normal control children could help in answering questions on whether having any risk factor affects the development of visual functions.

8.5. Strengths and limitations of this study

It should be acknowledged that this study was not without limitations. The major limitation of this study was the inability to include children who were born without having any perinatal risk factors. Inclusion of such children would have allowed us to assess the effect of being at risk of NH on visual development. However, as the main research question of the overall CHYLD study was to observe the effects of NH on neurodevelopment, study resources could not be allocated to the recruitment of control children. Such a control group could not be recruited specifically for this study either as this would have required access to detailed medical histories at the time of birth of those children. Without access to such information (including blood glucose testing results), it is very difficult to rule out the presence of any perinatal risk factors for neurodevelopment in a control group. This was not an issue for the CHYLD study cohort as all of the children had been recruited to randomized clinical trials at birth and therefore detailed perinatal data were available for each participant.

A second limitation of this study was imposed by the interdisciplinary nature of the CHYLD study where a series of neurodevelopmental assessments were conducted on a child in a single session. This meant that there was a time constraint placed on the testing of each developmental domain (cognition, vision etc.). We were, therefore, only able to implement a certain number of vision tests. A more robust eye examination including, cycloplegic refraction and fundoscopy (assessment of the posterior segment of eye) at both ages would have given a clearer picture of ocular development and more detailed information about any vision disorders in these children. For example it would have been very useful to know how well focused the eyes were and to be able to follow the development of refractive error from 2 to 4.5 years. Furthermore, the inclusion of a global form perception test and other more complex visual tasks that required higher level visual processing, such as figure ground segregation and biological motion would have allowed for a more thorough investigation of visual processing. Previous studies have suggested that higher visual functions may be severely affected while lower level visual functions such as visual acuity, contrast and even global motion and global form remain normal in children who had brain insults early in life (Knyazeva et al., 2002).

A third limitation of this study was imposed by the fact that the CHYLD study was composed of two cross-sectional studies for which testing methods had to be optimised accordingly. Ideally, a longitudinal study would involve same test at two ages but the use of age appropriate tests in our study was unavoidable as tests that are robust and have a high rate of testability for a particular age group had to be implemented. This process led us to utilise

a normalisation process, which has its own advantages and disadvantages. While the normalisation processed allowed us to transform the data obtained with different tests into a common metric (ratio) it also added some uncertainties such as change in variability of the data and lack of knowledge about the raw data and its spread.

Notwithstanding these limitations, the study had significant strengths. The study involved an internationally unique cohort of children and was the first to longitudinally assess the impact of neonatal hypoglycaemia on visual development. The study also had a large sample size and provided new information on the development of vision from 2 to 4.5 years of age.

8.6. Summary of the discussion

Taken together, despite having some limitations such as the use of age appropriate methods and the study being a part of a large multidisciplinary study (the CHYLD study), this study has generated some novels findings that were unexplored in the previous literature.

The CAC and the LS tests that we used for the preschool children enrolled in our study when tested in adult participants were reasonably related with one another. Moreover, under focused conditions, the bias between these two tests was close to the clinically accepted range of limits of agreement but changed proportionately under varying levels of defocus. Similar bias but a better correlation was observed between the two tests when they were compared in a small subset of 4.5-year-old children. The bias could be due to the inherent design of the vanishing optotypes. This finding helped us in explaining the higher prevalence of abnormal visual acuity at 4.5 years than at 2 years such that the CAC was insensitive in detecting abnormal vision at 2 years of age. These results motivated us to normalise the child data relative to adult thresholds. The normalised values provided information on the best achievable visual functions at each age and the magnitude of visual development from 2 to 4.5 years.

There was a considerable improvement in visual acuity, stereopsis and global motion perception from 2 years to 4.5 years of age however; adult levels were not attained for any of the visual functions measured, which signifies that these visual functions continue to develop beyond 4.5 years of age. Measures of visual function at 2 years were not predictive of visual outcome at 4.5 years, which indicated that caution must be exercised while interpreting measures taken at a young age. The weak relationship between the measures made at the two ages indicated that different mechanisms could be responsible for processing age appropriate tests even within a same domain. The development of binocular

visual acuity, stereopsis and global motion perception from age 2 years to 4.5 years was not affected by exposure to mild and moderate hypoglycaemia after birth. The most likely reason seemed to be due to appropriate treatment of the hypoglycaemic children as soon as they were detected.

Chapter 9. Conclusion

This chapter summarises the whole thesis with regard to the research hypotheses and findings and goes to report on the contribution of this thesis to the scientific literature. Furthermore, it provides a list of questions that could be addressed in future research. .

The key aims of this project were to track longitudinal development of binocular visual acuity, stereopsis and global motion perception from 2 to 4.5 years of age in children born at risk of neonatal hypoglycaemia (NH) and to observe the impact of neonatal hypoglycaemia on visual development. Knowledge of the effects of NH on visual development in the current literature is limited. This is because of the lack of a well-designed prospective, longitudinal study on this topic and because previous studies have focused only on overall neurodevelopment or obvious pathologies (Boluyt, van Kempen, & Offringa, 2006; Singh et al., 1991; Tam et al., 2012). Moreover, previous studies have mostly included children with severe hypoglycaemia (Kinnala et al., 1999; Murakami et al., 1999). The incidence of severe hypoglycaemia is rare in developed countries, as children born at risk are screened and promptly treated (McKinlay et al., 2014); hence, the understanding of mild to moderate hypoglycaemia (which is relatively common) on visual development was important to understand. The project that comprises this thesis was a part of a large interdisciplinary longitudinal prospective study, known as the CHYLD study, which involved more than 614 children, all born at risk of neonatal hypoglycaemia (McKinlay et al., 2015). Half of the children experienced mild to moderate hypoglycaemia in the neonatal period. The CHYLD study was a comprehensive study which included a well-matched child population that differed in just the presence or absence of neonatal hypoglycaemia so that the effect of NH could be isolated. The investigators were blind to the neonatal history of the children being examined. Furthermore, this thesis also explored the association between routinely used, standardized, age-appropriate clinical vision tests in adults as well as in children.

The aim of the first experiment reported in this thesis was to observe the relationship between the different paediatric visual acuity tests used with the CHYLD study children when administered in adults. This study enabled the comparison of the tests at a time when cognitive factors played a minimal role on their performance. An adult acuity chart was included in the comparison. In addition, the effect of spherical and astigmatic defocus on the visual acuity performance on various charts was also investigated. The findings of this study suggest that the Cardiff Acuity Chart (CAC; the acuity chart used at 2 years) and the Lea Symbols chart (LS; the acuity chart used at 4.5 years) are meaningfully related to one

another in adults. We proposed that an offset of 0.30 logMAR needed to be accounted for in order to optimize agreement between these two paediatric tests. The LS and the gold standard adult Early Treatment of Diabetic Retinopathy Study (ETDRS) chart agreed highly on their measures and were well-correlated with one another. Optical defocus acted differentially on the acuity performance obtained with different charts, whereby the CAC was least affected and the LS and ETDRS charts were most affected. This indicates that caution should be implemented while using the CAC in a population who have a high risk of developing refractive errors.

The aim of the second study reported in this thesis was to investigate the relationship between the measures of visual functions of children at 2 years and at 4.5 years of age. To achieve this goal, the longitudinal development and improvement in visual performance of the children from 2 years to 4.5 years of age was tracked relative to adult performance. The aspects of visual performance tracked in this manner were visual acuity, stereoscopic acuity and thresholds for global motion perception. The results of this investigation showed that there was a weak relationship between measures of visual acuity at 2 years and at 4.5 years of age. However, no consistent relationships existed between measures of global motion perception and stereopsis at 2 years and at 4.5 years of age. These findings indicated that a single test at two years is not sufficient to make decisions about long-term visual outcome in at-risk children. This is in agreement with previous experiments where no relationship was observed between acuity measures at a young age and at an older age (Hall et al., 2000; Clay Mash & Dobson, 1998). Furthermore, the most obvious finding to emerge from this study was that visual functions relative to adults improve considerably from 2 years of age to 4.5 years of age. The maximum improvement was observed for stereopsis, followed by global motion perception. An implication of this is the possibility that there is a rapid development of visual functions from 2 to 4.5 years of age and development during this period could be particularly prone to environmental factors such as visual experience.

The aim of the third and main investigation reported in this thesis was to explore the impact of mild to moderate neonatal hypoglycaemia on the development of binocular visual acuity, stereopsis and global motion perception from the age of 2 years to the age of 4.5 years. The longitudinal nature of the CHYLD study and the fact that the investigators were blind to the history of the child participants provided an excellent opportunity to study two related but separate aims. We found that the visual development of children who experienced mild/moderate neonatal hypoglycaemia, and who received treatment was no different from the visual development of those who did not have episodes of hypoglycaemia detected. There were no differences between the two groups of children in the development of binocular visual acuity, the development of stereopsis or in the development of global motion

perception. In addition, this part of the study showed that, even though the prevalence of visual disorders was higher at 4.5 years than at 2 years, having any experience of episodes of hypoglycaemia in the neonatal period did not affect the prevalence rate.

9.1. Research contribution

The work described in this thesis has implications that will be directly applicable not only to clinicians and researchers in optometry and vision science but also to a wider community of paediatric health care professionals. This is the first and the largest study comparing the development of essential visual functions from 2 to 4.5 years between children who did and who did not experience episodes of mild to moderate hypoglycaemia following birth. The present study makes several noteworthy contributions to the vision science and paediatric literature, and these are listed as follows:

1) The experiment conducted in adult participants provided a new understanding of the relationship between routinely used paediatric visual acuity tests (the CAC and the LS) and can serve as a base for future longitudinal studies of visual development that utilize these tests. The CAC overestimated VA by 0.3 logMAR, whereas the LS results were in good agreement with the gold standard ETDRS chart.

2) The normalization method (transforming paediatric measures into “development relative to adult thresholds”) used in our study may be applied to other visual development studies that use different (but age-appropriate) tests at different stages of development. Using age-appropriate tests in this way is desirable because it allows for the effects of cognitive development on longitudinal outcomes to be minimized.

3) The finding that measures of visual functions at 2 years of age and measures of visual functions at 4.5 years of age were either not correlated at all or only weakly correlated indicates that measures made at 2 years do not appear to predict those made at 4.5 years.

4) The effect of episodes of neonatal hypoglycaemia on the development of visual functions from 2 to 4.5 years of age that we have shown in this study assists our understanding of the role that mild to moderate hypoglycaemia at birth has on subsequent development. In regard to visual development, it can be confidently stated that early and appropriate treatment of NH according to the current clinical practice guidelines is effective in allowing development of normal visual function up until 4.5 years of age as long as blood glucose level targets in the neonatal period are kept above the 2.6mmol/L level.

9.2. Scope for future research

This research has generated a number of questions that are in need of further investigation. These can be discussed in several points as follows:

a) Does the same weak relationship between visual acuity tests exist in a population with high prevalence of refractive error or visual impairment?

This study determined that there was a weak but statistically significant relationship between the Cardiff Acuity Cards and the Lea Symbols when these tests were implemented in a group of children who had low prevalence of refractive errors and reduced vision. It is unclear if the same relationship exists in children with a high prevalence of refractive errors and visual impairment. Implementation of these tests in a group of children who are at risk of developing refractive error and visual impairment will help us to better understand the relationship between the tests.

b) Can we predict long-term visual outcome by the use of the same test at 2 years and at 4.5 years, unlike this study which used age-appropriate tests at two different ages?

This study demonstrated that when using age appropriate visual function tests at two different ages, the measure of visual function at a younger age does not predict long term visual outcome. It is interesting to consider whether the use of the same test at two different ages would be predictive of long-term visual outcome. However, previous studies that have used same test of visual acuity at two different ages have reported weak to moderate relationship between tests. (Dobson et al., 1999; Hall et al., 2000; Mash & Dobson, 1998)

c) Are other visual functions, besides visual acuity, stereopsis and global motion perception, such as biological motion, global form perception and contrast sensitivity affected by neonatal hypoglycaemia?

Only three domains of visual function (visual acuity, stereopsis and global motion perception) were assessed in this study. As neonatal hypoglycaemia sometimes may cause widespread brain injuries, which may include the frontal lobe and the basal ganglia of the brain, it is possible that other domains of visual function such as contrast sensitivity, biological motion perception and global form perception might be affected. Another study that incorporates measures of these visual functions will allow us to observe if these domains of visual function are affected by neonatal hypoglycaemia.

d) What are the effects of severe hypoglycaemia (<2.00mmol/L) on visual development?

One of the reasons that the hypoglycaemic children in our study did not exhibit any differences in visual function compared to the euglycaemic group could be that they experienced only mild to moderate levels of hypoglycaemia. Previous studies that have reported visual deficits have included children who experienced severe hypoglycaemia. Implementation of detailed visual assessment tests in a cohort of children that includes a considerable proportion of children who experienced severe hypoglycaemia after birth would allow us to understand the effect of severe hypoglycaemia on different visual functions.

e) Do visual deficits in children with a history of hypoglycaemia develop later than 4.5 years of age?

This study followed up children until the age of 4.5 years. It is possible that visual deficits may become apartment in later childhood when advanced visual functions are mature. Further follow up of these children until adulthood would address this question.

These are questions that could be addressed in future research in order to gain a better understanding of the development of visual functions in children and whether neonatal hypoglycaemia may still have effects on visual development that do not appear until after 4.5 years of age.

9.3. Take home messages of this study

Three major findings from this study need to be highlighted. They are as follows:

Stereoacuity shows the most pronounced development from 2 to 4.5 years of age followed by global motion perception and binocular visual acuity.

Caution must be exercised when extrapolating measures of visual or stereoacuity made using the Cardiff Acuity Cards and the Lang or Frisby stereo tests at 2 years of age for long-term visual outcome.

Early detection and appropriate treatment of neonatal hypoglycaemia under the current clinical practice guidelines appears to allow for normal development of binocular visual acuity, stereopsis and global motion perception until 4.5 years of age.

Appendices:

Publications related to this thesis:

Yu, T. Y., Jacobs, R. J., Anstice, N. S., **Paudel, N**., Harding, J. E., & Thompson, B. (2013). Global motion perception in 2-year-old children: a method for psychophysical assessment and relationships with clinical measures of visual function. *Investigative Ophthalmology & Visual Science*, 54(13), 8408.

McKinlay C.J.D., Alsweiler, J.M., Ansell J.M., Anstice, N.S., Chase J,G., Gamble, G.D., Harris, D.L., Jacobs, R.J., Jiang, Y., **Paudel, N**., Signal, M., Thompson, B., Wouldes, T.A., Yu, TY., Harding, J.E. (2015) .Neonatal Glycemia and Neurodevelopmental Outcomes at Two Years. *New England Journal of Medicine*, In Press

Conference presentations related to this thesis:

Paudel, N., Sloan, R., Anstice, N.S., Thompson, B., Jacobs, R.J. Differential effect of optical defocus on Cardiff, Lea, and ETDRS acuity in adult observers. Poster Presentation delivered at Asia-ARVO, New Delhi, India, November 2013.

Paudel, N., Jacobs, R.J., Thompson, B., Yu, TY., Chakraborty, A., Anstice, N.A. on behalf of the CHYLD Study Group. Do age appropriate clinical vision tests at 2 years predict visual outcome at 4.5 years? Poster presentation delivered at American Academy of Optometry Meeting, Denver, Colorado, November 2014.

Paudel, N., Anstice, N.S., Chakraborty, A., Jacobs, R.J., Yu, TY., Harding, J.E and Thompson, B on behalf of the CHYLD Study Group. Development of global motion processing and binocular visual acuity from 2 to 4.5 years of age in children born with perinatal risk factors. Paper presentation at the Child Vision Research Society Meeting, Prague, Czech Republic, June, 2015.

CHYLD two year old vision assessment form:

Sticker for patient details:

Name, Study ID, Age/Birth dates

CHYLD Study Vision Assessment Recording Form

Gender of child: m / f
Date of assessment: ____/____/_____
Time of day of assessment: Morning [m] / Afternoon [a]
Order of assessment: Before / After psychological assessment
Assessor name:_____ [assessor initials]

Gross observation of the mood/state of the child: _____

	Comments/Clinical Notes /Test Results	Data Title Explanation for data coding /entry	Data (code or circle)
Motion Coherence Threshold ☐ did not attempt ☐ would not co-operate	**Training** ☐ did not attempt training [-2] ☐ no behavioural response/failed training [-1] ☐ 1 dot training [1] ☐ 250 dots training [2]	**Training Achievement level** [code]	
	Single dot tracking eye movements: Yes / No	**Local motion eye tracking**	y / n
	Threshold programme Number of trial sets run: _____ Pictures used:_____	**Threshold programme attempt** ys = Yes, successful yu=Yes, unsuccessful n =No	ys / yu / n
	Test duration [secs] [ ]	**Test duration** [code]	
	No. of trials completed: [ ]	**No. of trials completed** [code]	
	Behavioural responses given: Yes [y] / No [n]	**Behavioural responses given** [code]	y / n

Health – Internal ☐ did not attempt ☐ would not co-operate	**Red reflex/ Bruckner test and Corneal reflexes** ☐ *normal red reflexes* ☐ absent, abnormal, asymmetric red reflex ☐ cataract: R/ L / B ☐ leukocoria: R / L / B ☐ coloboma: R / L / B ☐ inflammation: R / L / B ☐ malformations: R / L / B ☐ suspect anisometropia / strabimus (record under binocularity) ☐ other abnormalities:_____	**Attempt at Red reflex** ys = Yes and successful yu=Yes, unsuccessful n =No	ys / yu / n
		Normal Red Reflex y = Yes no= no unilateral nb = bo bilateral	y / no / nb
		Cataract n =No u = unilateral b = bilateral	n / u / b
		Retinal pathology n =No u = unilateral b = bilateral	n / u / b
		Internal Tumour n =No u = unilateral b = bilateral	n / u / b
		Inflammation n =No u = unilateral b = bilateral	n / u / b
		Malformations n =No u = unilateral b = bilateral	n / u / b
		Other internal abnormalities n =No u = unilateral b = bilateral	n / u / b
☐ did not attempt ☐ would not co-operate	**Pupillary reaction** ☐ *normal pupil shape* ☐ *normal pupillary reaction* ☐ abnormal pupil shape: R / L / B ☐ abnormal pupillary reflex: R / L Direct / Consensual / RAPD ☐ anisocoria, larger pupil is : R / L	**Attempt at pupil examination** ys = Yes and successful yu=Yes, unsuccessful n =No	ys / yu / n
		Normal pupil shape y =Yes no = one abn nb = both abn	y / no / nb
		Direct Pupil Reflexes ben = both normal bea = both abnormal oea = one abnormal	ben / bea / oea
		Consensual Pupil Reflexes ben = both normal bea = both abnormal oea = one abnormal	ben / bea / oea
		RAPD n = No RADP in either eye y = RADP present	n / y
		Pupil Anisocoria n = No anisocoria y = anisocoria	n / y
	Internal Health Referred y = Yes n =No		n / y

Health – External Ocular inspection ☐ did not attempt ☐ would not co-operate	☐ *symmetry of lids* ☐ *no ocular irritation* ☐ *no obvious abnormalities* ☐ ptosis: R / L / B ☐ abnormal head posture: R / L Turn / Tilt Chin tilt Up / Down ☐ redness: R / L / B ☐ discharge: R / L / B ☐ corneal opacity: R / L / B ☐ tumour or abnormal growth: R / L / B ☐ microphthalmos: R / L / B ☐ other external/anterior segment pathology:_____	**Attempt at external ocular inspection** ys = Yes and successful yu=Yes, unsuccessful n =No	ys / yu / n
		Ptosis n = no u = unilateral b = bilateral	n / u / b
		Normal Head posture y = Yes n =No	y / n
		Redness n = no u = unilateral b = bilateral	n / u / b
		Discharge n = no u = unilateral b = bilateral	n / u / b
		Corneal opacity n = no u = unilateral b = bilateral	n / u / b
		External tumour n = no u = unilateral b= bilateral	n / u / b
		Microphthalmos n = no u = unilateral b = bilateral	n / u / b
		Other external/anterior segment pathology n = no u = unilateral b = bilateral	n / u / b
		External Health Referred y = Yes n =No	n / y

	Comments/Clinical Notes /Test Results	Data Title Explanation for data coding /entry	Data (code or circle)
Strabismus ☐ did not attempt ☐ would not co-operate	**Cover test** ☐ *Both eyes straight (no movement)* ☐ Tropia: R / L / Alternating ESO/ EXO / HYPER	**Attempt at Cover test** ys = Yes, successful yu=Yes, unsuccessful n = No	ys / yu / n
		Attempt at Hirschberg Corneal reflexes ys = Yes, successful yu=Yes, unsuccessful n = No	ys / yu / n
		Direction of Heterotropia n = no heterotropia exo = exotropia eso = esotropia hyper = hypertropia	n / exo / eso / hyper / hypo
☐ did not attempt ☐ would not co-operate	**Hirschberg Corneal reflexes** ☐ *Normal symmetrical corneal reflexes* ☐ Asymmetric corneal reflexes : R / L ESO / EXO / HYPER	**Which eye has tropia** n = no r = right l = left a = alternating	n / r / l / a
☐ would not co-operate ☐ did not attempt	**Prism Cover test**: [ ] R / L **Krimsky's prism test**: [ ] R / L	**Attempt at Quantifying deviation** ys = Yes, successful yu=Yes, unsuccessful n = No	n / ys / yu
		Size of deviation [code]	
		Binocularity Referred y = Yes n =No	n / y

Suppression Motor Fusion ☐ would not co-operate ☐ did not attempt	**20ΔPrism Test** ☐ *Fixation movement seen both eyes* ☐ *Fusion movement seen both eyes* ☐ suppression: R / L / Alternating ☐ lack of fusion: R / L / B	**Attempt at Suppression/Motor fusion test** ys = Yes and successful yu=Yes and unsuccessful n =No	ys / yu / n
		Suppression n =No y = Yes	n / y
		Fusion y = Yes n =No	y / n

Motility/ Smooth pursuit and NPC ☐ would not co-operate ☐ did not attempt	☐ *normal motility* ☐ *normal smooth pursuit* ☐ *normal NPC (≤ 15cm)* ☐ abnormal tracking: no tracking / inaccurate / unsmooth / slow ☐ nystagmus ☐ muscle weakness:_____ ☐ muscle restriction:_____ ☐ abnormal NPC (>15cm)	**Attempt at Motility/Smooth pursuits and NPC** ys = Yes and successful yu=Yes and unsuccessful n =No	ys / yu / n
		Motility normal = normal motility (versions and ductions) weak = muscle weakness restrict = muscle restriction	normal / weak / restrict
		Smooth pursuit normal = normal smooth tracking absent = no tracking inaccu = tracking inaccurate unsmooth = tracking not smooth slow = fails to keep up with target	normal / absent / inaccu / slow / unsmooth
		Nystagmus n = no u = unilateral b = bilateral	n / u / b
		Normal NPC y = Yes (≤15cm) n =No (>15cm)	y / n
		Motility Referred y = Yes (muscle weakness or restriction, nystagmus) n =No	n / y

Stereopsis	☐ present with Frisby plates: Plate no:____ @ _____cm [ ] ″ ☐ did not attempt ☐ could not perform Frisby plates	**Attempt at Frisby** ys = Yes and successful u=Yes and unsuccessful n =No	ys / yu / n
		Frisby stereopsis [code]	
	☐ present with Lang stereotest: Picture:_____ Lang I / Lang II [ ] ″ ☐ did not attempt ☐ could not perform Lang I and II stereotest	**Attempt at Lang tests** ys = Yes and successful yu=Yes and unsuccessful n =No	ys / yu / n
		Lang tests stereopsis [code]	

	Comments/Clinical Notes /Test Results	Data Title Explanation for data coding /entry	Data (code or circle)
Visual Acuity Aided / Unaided	Objection To Obstruction: No [n] / R only [r] / L only [l] / Both eyes [b]	**Objection to Obstruction** [code]	n / r / l / b
	Cardiff Cards @Distance = _____ R _____ [ ] logMAR L _____ [ ] LogMAR BE _____ [ ] LogMAR (to nearest 2 decimal places) ☐ did not attempt ☐ could not perform Cardiff cards : R / L / B	**Attempt at Cardiff Cards** ysu = Yes and successful unilateral both eyes only ysur = Yes and successful unilateral right eye only ysul = Yes and successful unilateral left eye only ysb = Yes and successful bilateral only ysub = Yes and successful bilateral and unilateral yu=Yes and unsuccessful n =No	ysu / ysur / ysul / ysb / ysub / yu / n
		RE Cardiff [code]	
		LE Cardiff [code]	
		BE Cardiff [code]	
	Teller Acuity Cards @Distance = _____ R _____ [ ] LogMAR L _____ [ ] LogMAR BE _____ [ ] LogMAR (to nearest 2 decimal places) ☐ did not attempt ☐ could not perform Teller cards: R / L / B	**Attempt at Teller Acuity Cards** ysu = Yes and successful unilateral both eyes ysur = Yes and successful unilateral right eye only ysul = Yes and successful unilateral left eye only ysb = Yes and successful bilateral only ysub = Yes and successful bilateral and unilateral yu=Yes and unsuccessful n =No	ysu / ysur / ysul / ysb / ysub / yu / n
		RE Teller [code]	
		LE Teller [code]	
		BE Teller [code]	

Retinoscopy	R _____ ☐ did not attempt ☐ would not co-operate		**Attempt at Retinoscopy Right eye** ys = Yes, successful yu=Yes, unsuccessful n =No	ys / yu / n
		RE M [ ] D	**Retinoscopy RE M** [code] (to nearest 2 d.p)	
		RE J0 [ ] D	**Retinoscopy RE J0** [code] (to nearest 2 d.p)	
		RE J45] D	**Retinoscopy RE J45** [code] (to nearest 2 d.p)	
	L _____ ☐ did not attempt ☐ would not co-operate		**Attempt at Retinoscopy Left eye** ys = Yes, successful yu=Yes, unsuccessful n =No	ys / yu / n
		LE M [ ] D	**Retinoscopy LE M** [code] (to nearest 2 d.p)	
		LE J0 [ ] D	**Retinoscopy LE J0** [code] (to nearest 2 d.p)	
		LE J45] D	**Retinoscopy LE J45** [code] (to nearest 2 d.p)	
	☐ Referred	☐ Anisometropia ≥1D ☐ Astigmatism ≥1.5D ☐ Myopia ≥ 2D ☐ Hyperopia ≥3.5D	**Retinoscopy Referred** n =No aniso = referral due to anisometropa ≥ 1D astig = referral due to astigmatism ≥ 1.5D myopia = referral due to myopia ≥ 2D hyperopia = referral due to hyperopia ≥ 3.5D	n / aniso / astig / myopia / hyper

Auto-refractor	R _____ Confidence : _____ ☐ did not attempt ☐ would not co-operate		**Attempt at Auto-refraction Right eye** ys = Yes, successful yu=Yes, unsuccessful n =No	ys / yu / n
		RE M [ ] D	**Auto-refractor RE M** [code] (to nearest 2 d.p)	
		RE J0 [ ] D	**Auto-refractor RE J0** [code] (to nearest 2 d.p)	
		RE J45 [ ] D	**Auto-refractor RE J45** [code] (to nearest 2 d.p)	
	L _____ Confidence : _____ ☐ did not attempt ☐ would not co-operate		**Attempt at Auto-refraction Left eye** ys = Yes, successful yu=Yes, unsuccessful n =No	ys / yu / n
		LE M [ ] D	**Auto-refractor LE M** [code] (to nearest 2 d.p)	
		LE J0 [ ] D	**Auto-refractor LE J0** [code] (to nearest 2 d.p)	
		LE J45 [ ] D	**Auto-refractor LE J45** [code] (to nearest 2 d.p)	

REFERRAL	YES / NO	Ocular motility / Strabismus / Pathology / Refraction	**Referral** n = no referral needed refpath = pathology refmot = ocular motility abnormalities refstrab = strabismus refrefra = refraction outside acceptable limits	n / refpath / refmot / refstrab / refrefra

Assessor signature: _____ Date: _____

CHYLD 4.5-year-olds vision assessment form:

Vision Assessment Recording form (4.5 year-old participants)

Name initial: _____

Study ID: _____

Gender of child: ☐ F ☐ M

Date of assessment:

Time of day of assessment:

Order of assessment: Before / After psychological assessment

Gross observation of the mood/state of the child: _____
_____
_____

	Comments/Clinical Notes /Test Results	**Data Title** Explanation for data coding /entry	**Data (code or circle)**
Assessor	Name: **Arijit Chakraborty / Nabin Paudel / Nicola Anstice**	**Assessor** [code] AC / NP / NA	

	Comments/Clinical Notes /Test Results		**Data Title** Explanation for data coding /entry	Data (code or circle)
Motion Coherence Threshold	**Training *(4.5 years program)*** ☐ did not attempt training [-2] ☐ no behavioural response/failed training [-1] ☐ 100 dots training [2]		**Training Achievement level** [code] ***Notes:*** *Go to the next section "**Training (2 years program)**" if the code is **-1***	-2 / -1 / 2
	Training *(2 years program)* *[only if 4.5 years training fails]* ☐ did not attempt training [-22] ☐ no behavioural response/failed training [-21] ☐ 1 dot training [21] ☐ 250 dots training [22]		**Training Achievement level** [code] ***Notes:*** *Go to the "**Motion Coherence Threshold 2 years program**" section next if you have done this training*	-22 / -21 / 21 / 22
Motion Coherence Threshold *4.5 years program* ☐ did not attempt ☐ did not co-operate	**Threshold program** Attempt at threshold programme: Yes / No Cooperation from child: Yes / No		**Threshold programme attempt** ys = Yes and successful yu=Yes and unsuccessful n =No	ys / yu / n
	Test duration (including short breaks)	[ ]secs	**Test duration** [code]	
	Behavioural threshold	[ ]%	**Behavioural threshold** [code]plot	
	Standard error of behavioural threshold	[ ]%	**SE of behavioural threshold** [code]	
	No. of trials with behavioural response	[ ]	**No. of trials with behavioural response** [code]	
Motion Coherence Threshold *2 years program* ☐ did not attempt ☐ did not co-operate	Single dot tracking eye movements: Yes / No		**Local motion eye tracking**	y / n
	Threshold program Number of trial sets run: _____ Pictures used: _____		**Threshold programme attempt** ys = Yes and successful yu=Yes and unsuccessful n =No	ys / yu / n
	Test duration [secs]	[ ]	**Test duration** [code]	
	No. of trials completed:	[ ]	**No. of trials completed** [code]	
	Behavioural responses given: Yes [y] / No [n]		**Behavioural responses given** [code] [-99] if no PF plot	y / n

	Comments/Clinical Notes /Test Results	Data Title Explanation for data coding /entry	Data (code or circle)
Ocular Health ☐ did not attempt ☐ did not co-operate	**Pupillary reaction** ☐ *normal pupil shape* ☐ *normal pupillary reaction* ☐ abnormal pupil shape: R / L / B ☐ abnormal pupillary reflex: R / L Direct / Consensual / RAPD ☐ anisocoria, larger pupil is : R / L	**Attempt at pupil examination** ys = Yes and successful yu=Yes and unsuccessful n =No	ys / yu / n
		Normal pupil shape y =Yes no = one pupil abnormal nb = both pupils abnormal	y / no / nb
		Direct Pupil Reflexes ben = both eyes normal direct pupil reaction bea = both eyes abnormal direct pupil reaction oea = one eye abnormal direct pupil reaction	ben / bea / oea
		Consensual Pupil Reflexes ben = both eyes normal consensual pupil reaction bea = both eyes abnormal consensual pupil reaction oea = one eye abnormal direct pupil reaction	ben / bea / oea
		RAPD n = No RADP in either eye y = RADP present	n / y
		Pupil Anisocoria n = No anisocoria y = anisocoria present	n / y
☐ did not attempt ☐ did not co-operate	**Red reflex / Bruckner test** ☐ *normal red reflexes* ☐ absent, abnormal, asymmetric red reflex ☐ leukocoria: R / L / B	**Attempt at Red reflex** ys = Yes and successful yu=Yes, unsuccessful n =No	ys / yu / n
		Normal Red Reflex y = Yes no= no unilateral nb = no bilateral	y / no / nb

	Comments/Clinical Notes /Test Results	Data Title Explanation for data coding /entry	Data (code or circle)
☐ did not attempt ☐ did not co-operate	**External Ocular Inspection** ☐ *symmetry of lids* ☐ *no ocular irritation* ☐ *no obvious abnormalities* ☐ ptosis: R / L / B ☐ abnormal head posture: R / L Turn / Tilt Chin tilt Up / Down ☐ redness: R / L / B ☐ discharge: R / L / B ☐ corneal opacity: R / L / B ☐ tumour or abnormal growth: R / L / B ☐ microphthalmos: R / L / B ☐ other external/anterior segment pathology: _____ _____ _____ _____	**Attempt at external ocular inspection** ys = Yes and successful yu=Yes and unsuccessful n =No	ys / yu / n
		Ptosis n = no ptosis of either eye u = unilateral ptosis b = bilateral eyes have ptosis	n / u / b
		Normal Head posture y = Yes n =No	y / n
		Redness n = no redness of either eye u = unilateral redness b = bilateral redness	n / u / b
		Discharge n = no discharge from either eye u = unilateral discharge b = bilateral discharge	n / u / b
		Corneal opacity n = no corneal opacity u = unilateral corneal opacity b = bilateral corneal opacities	n / u / b
		External tumour (any) n = no pathological abnormal growths u = unilateral pathological abnormal growth(s) b = bilateral pathological abnormal growths	n / u / b
		Microphthalmos (abnormal smallness of one or both eyes) n = No u = unilateral microphthalmos b = bilateral microphthalmos	n / u / b
		Other external/anterior segment pathology (any pathology of the lids or anterior segment) n = No u = unilateral other external pathology b = bilateral other external pathology	n / u / b

	Comments/Clinical Notes /Test Results	Data Title Explanation for data coding /entry	Data (code or circle)
Strabismus ☐ did not attempt ☐ did not co-operate	**Cover test** ☐ *Both eyes straight (no movement)* ☐ Tropia: R / L / Alternating ESO/ EXO / HYPER ☐ Tropia: Distance / Near / Intermediate **Hirschberg Corneal reflexes** ☐ *Normal symmetrical corneal reflexes* ☐ did not attempt ☐ would not co-operate ☐ Asymmetric corneal reflexes : R / L ESO / EXO / HYPER	**Attempt at Cover test** ys = Yes and successful yu=Yes and unsuccessful n = No (performed Hirschberg reflexes to determine binocularity)	ys / yu / n
		Attempt at Hirschberg Corneal reflexes ys = Yes and successful yu=Yes and unsuccessful n =No	ys / yu / n
		Direction of Heterotropia n = no heterotropia exo = exotropia eso = esotropia hyper = hypertropia	n / exo / eso / hyper / hypo
		Which eye has tropia n = no heterotropia r = right heterotropia l = left heterotropia a = alternating heterotropia	n / r / l / a
Motor Fusion ☐ did not attempt ☐ did not co-operate	**(20Δ BO Prism) Test at near** ☐ *Fixational movement seen in both eyes* ☐ *Fusional movement seen in both eyes* ☐ lack of fusion: R / L / B	**Attempt at Motor fusion test** ys = Yes and successful yu=Yes and unsuccessful n =No	ys / yu / n
		Fusion y = Yes n =No	y / n
Motility/ Tracking and NPC ☐ did not attempt ☐ did not co-operate	☐ *normal motility* ☐ *normal smooth pursuit* ☐ *normal NPC (≤ 15cm)* ☐ abnormal tracking: no tracking / inaccurate / unsmooth / abnormally slow ☐ nystagmus ☐ muscle weakness:_____ _____ ☐ muscle restriction:_____ _____ ☐ abnormal NPC (>15cm)	**Attempt at Motility/Smooth pursuits and NPC** ys = Yes and successful yu=Yes and unsuccessful n =No	ys / yu / n
		Motility normal = normal motility (versions and ductions) weak = muscle weakness restrict = muscle restriction	normal / weak / restrict
		Smooth pursuit normal = normal smooth tracking absent = no tracking eye movements inaccu = tracking inaccurate unsmooth = tracking not smooth slow = fails to keep up with target	normal / absent / inaccu / slow / unsmooth
		Nystagmus n =No u= unilateral nystagmus b= bilateral nystagmus	n / u / b
		Normal NPC y = Yes (≤15cm) n =No (>15cm)	y / n
Sensory Suppression ☐ did not attempt ☐ did not co-operate	**Randot Stereotest with R/L box** ☐ *fusion* ☐ suppression: R / L / Alternating	**Attempt at Sensory suppression test** ys = Yes and successful yu=Yes and unsuccessful n =No	ys / yu / n
		Suppression y = Yes n =No	n / y

	Comments/Clinical Notes /Test Results	Data Title Explanation for data coding /entry	Data (code or circle)
Stereopsis ☐ did not attempt ☐ did not co-operate	☐ *present with Randot stereotest [ ]"* ☐ present with Lang stereotest Picture:_____ Lang I / Lang II [ ]" ☐ present with Frisby stereotest Plate no:____ @ _____cm [ ]"	**Attempt at Randot** ys = Yes and successful yu=Yes and unsuccessful n =No	ys / yu / n
		Randot: RAN Lang: LAN Frisby: FRI	RAN / LAN / FRI
		Stereopsis [code]	
Visual Acuity Aided / Unaided	Objection To Obstruction: No [n] / R only [r] / L only [l] / Both eyes [b]	**Objection to Obstruction** [code]	n / r / l / b
	Test Used: ☐ *Crowded Lea Symbol (single line)* / ☐ Crowded Lea Symbol (single optotype) ☐ *Sheridan Gardiner (crowded)* / ☐ Sheridan Gardiner (uncrowded)	**Test Used:** CLS-SL: Crowded Lea Symbol (single line) / *CLS-SO: Crowded Lea Symbol (single optotype)* SG-C: Sheridan Gardiner (crowded) / *SG-UC: Sheridan Gardiner (uncrowded)* ***Notes:*** *CLS-SO and SG-UC are alternate tests for CLS-SL and SG-C respectively*	CLS-SL / CLS-SO / SG-C / SG-UC / CC
	☐ Cardiff Cards	CC : Cardiff Cards ***Notes:*** *Do only if the code is "yu" in Crowded Lea & Sheridan Gardiner*	
☐ did not attempt ☐ did not co-operate R / L / B	***Crowded Lea Symbol*** R _____ [ ] logMAR L_____ [ ] LogMAR BE _____ [ ] LogMAR	**Attempt at Visual Acuity** ysur = Yes and successful right eye ysul = Yes and successful left eye ysb = Yes and successful bilateral only yu=Yes and unsuccessful n =No	ysur / ysul / ysb / yu / n
		RE Vision logMAR [code]	
		LE Vision logMAR [code]	
		BE Vision logMAR [code]	
☐ did not attempt ☐ did not co-operate R / L	***Sheridan Gardiner*** R _____ [ ] logMAR L_____ [ ] LogMAR	**Attempt at Visual Acuity** ysur = Yes and successful right eye ysul = Yes and successful left eye yu=Yes and unsuccessful n =No	ysur / ysul / yu / n
		RE Vision logMAR [code]	
		LE Vision logMAR [code]	
Only if the code is "yu" in both Crowded Lea and Sheridan Gardiner			
☐ did not attempt ☐ did not co-operate R / L / B	**Cardiff Cards** @Distance = _____ R _____ [ ] logMAR L_____ [ ] LogMAR BE _____ [ ] LogMAR (to nearest 2 decimal places)	**Attempt at Visual Acuity** ysur = Yes and successful right eye ysul = Yes and successful left eye ysb = Yes and successful bilateral only yu=Yes and unsuccessful n =No	ysur / ysul / ysb / yu / n
		RE Vision Cardiff [code]	
		LE Vision Cardiff [code]	
		BE Vision Cardiff [code]	

Auto-refractor ☐ did not attempt ☐ did not co-operate	R _____ Confidence : _____		**Attempt at Auto-refraction Right eye** ys = Yes, successful yu=Yes, unsuccessful n =No	ys / yu / n
		RE M [ ] D	**Auto-refractor RE M** [code] (to nearest 2 d.p)	
		RE J0 [ ] D	**Auto-refractor RE J0** [code] (to nearest 2 d.p)	
		RE J45 [ ] D	**Auto-refractor RE J45** [code] (to nearest 2 d.p)	
☐ did not attempt ☐ did not co-operate	L _____ Confidence : _____		**Attempt at Auto-refraction Left eye** ys = Yes, successful yu=Yes, unsuccessful n =No	ys / yu / n
		LE M [ ] D	**Auto-refractor LE M** [code] (to nearest 2 d.p)	
		LE J0 [ ] D	**Auto-refractor LE J0** [code] (to nearest 2 d.p)	
		LE J45 [ ] D	**Auto-refractor LE J45** [code] (to nearest 2 d.p)	

Contrast Threshold (RDK) ☐ did not attempt ☐ did not co-operate	**Contrast threshold training program** Attempt at training programme: Yes / No		ys = Yes and successful yu=Yes and unsuccessful n =No	ys / yu / n
	Contrast threshold test program Attempt at test programme: Yes / No Cooperation from child: Yes / No		ys = Yes and successful yu=Yes and unsuccessful n =No	ys / yu / n
	Contrast threshold	[ ]%	**Contrast threshold** [code]	
	Standard deviation of contrast threshold	[ ]%	**Standard deviation of contrast threshold** [code]	
	Number of trials in threshold measurement	[ ]	**Number of trials** [code]	

REFERRAL	YES / NO	Pathology / Ocular motility / Strabismus / Vision	**Referral** n = no referral needed refpath = pathology refmot = ocular motility abnormalities refstrab = strabismus refvis = visual acuity outside acceptable limits	n / refpath / refmot / refstrab / refvis

Referral Comments: _____

_____

_____

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