Characteristics and impact of nystagmus on visual acuity and eye movements in children with and without Down's syndrome

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ABSTRACT

Nystagmus, an involuntary oscillation of the eye, is one of the most common visual impairments occurring in individuals with Down's syndrome, affecting between 15-30% of that population. In the typical population, nystagmus affects 0.02% of children. Due to the frequent occurrence of nystagmus in Down's syndrome, nystagmus often appears to be assumed to be part of the condition and overlooked in this population of children. This study was designed to determine whether nystagmus is, in fact, the same or a different condition in children with and without Down's syndrome.

First, we investigated the visual characteristics of children with Down's syndrome with and without nystagmus, by retrospectively reviewing clinical records of 198 children in the Down's Syndrome Vision Research Unit cohort between 1992 and 2016. To compare the characteristics of nystagmus waveforms and the visual characteristics, we then conducted optometric assessments and recorded eye movements on 28 children with Down's syndrome and 17 typically developing children with nystagmus. Further to this, we recorded the eye movements of both groups of children with nystagmus along with 20 children with Down's syndrome and 20 typical children with no nystagmus while fixating on a stationary and a moving target. The aim was to characterize and compare the accuracy and precision of eye movements during fixation and when following a moving target for each group of children.

The findings from this study suggest that nystagmus in children with Down's syndrome is not a different condition from nystagmus in typically developing children. In addition, nystagmus has similar effects on visual acuity and eye movement performance in both groups of children with nystagmus. Therefore, children with Down's syndrome and nystagmus should receive the same level of attention from health and education services that typical children with nystagmus do.

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ABBREVIATIONS

AC	Alternating current
ANCOVA	Analysis of covariance
ATR	Against-the-rule
BVA	Binocular visual acuity
CI	Confidence intervals
cm	Centimeter
deg2	Degree squared
DS	Down's syndrome
DSN	Down's syndrome with nystagmus
e.g.	Example
EMR	Eye movement recording
EOG	Electro-oculography
EP	Eye position
etc.	Etcetera
FMNS	Fusion maldevelopment nystagmus syndrome
IN	Infantile nystagmus
inf	Infinity
INS	Infantile nystagmus syndrome
LE	Left eye
logMAR	Logarithm of minimum angle of resolution
mm	Millimeter

MRI	Magnetic resonance imaging
OA	Orthoptic assessment
OBL	Oblique
PDF	Probability density function
PL	Preferential looking
POG	Photo-oculography
RE	Right eye
Rx	Refractive error
SD	Standard deviation
sec	Second
SER	Spherical equivalent
SN	Spasmus nutans
SP	Smooth pursuit
T	Typically developing children
TM	Trademark
TN	Typically developing children with nystagmus
VA	Visual acuity
VEP	Visual evoked potential
WTR	With-the-rule

CHAPTER 1 INTRODUCTION

1.1 Introduction

Nystagmus is an involuntary eye movement that may onset in early childhood or even later in life. The prevalence of nystagmus in children has been reported to be 16.6 per 10,000 population (Sarvananthan et al. 2009). Typically developing children with nystagmus will generally be recognized as visually impaired. Therefore, we expect parents will be informed of the visual impact of nystagmus at diagnosis. We also expect the children to receive additional support in school through the Education Authority's Visual Impairment Service.

Nystagmus is also very common in children with Down's syndrome (Averbuch-Heller et al. 1999; Kim et al. 2002; Paudel et al. 2010; Ljubic et al. 2015). In fact, nystagmus is one of the major causes of visual function abnormalities found in people with Down's syndrome after uncorrected refractive error, strabismus and limited accommodation. Records of children attending the Cardiff University Special Assessment Clinic from November 2016 until February 2019 show 42 children with Down's syndrome and nystagmus (including 26 children who took part in the present study) were seen. The following points were established from the clinic notes of those children:

a) 1 child had thorough investigations of nystagmus (e.g. MRI, VEP, etc.)
b) 8 children were supported by their local Visual Impairment services and
c) 11 parents were not given any information on the impact of nystagmus on their child's vision
d) 2 parents were told that nystagmus was part of DS and "nothing to worry about"

(Woodhouse 2019, personal communication)

This is anecdotal evidence which triggered my interest to explore further the characteristics of nystagmus on children with and without Down's syndrome and investigate whether the waveforms revealed an important difference. The study was designed to answer the questions: 1) Is nystagmus a different or the same condition in Down's syndrome and typically developing children and 2) should nystagmus receive the same level of attention from health and education services in children with DS as it does in typical children? These questions were then addressed by, first looking at the visual acuity of the two groups of children, then by comparing the nystagmus waveforms and eye movement performance during fixation and smooth pursuit. The present chapter provides an overview of nystagmus and its impact on the visual function and different eye movements.

1.2 Nystagmus

1.2.1 Definition

Nystagmus was derived from the Greek word "*nustagmos*" which means nodding or drowsiness (Hertle and Dell'Osso 2013). When a person is sleepy, their head will slowly drift downward and snap up again to stay awake, and the process repeats itself. The same pattern, in the context of eye movements, is sometimes seen in nystagmus (Wong 2008). Nystagmus, by definition, is an involuntary rhythmic movement of the eyes, which is typically largely horizontal, i.e. swinging to and fro. It can be caused by lesions of the pursuit, optokinetic and vestibular system that disrupts the maintenance of fixation stability (Scheiman and Wick 2008). Nystagmus can present early in life (early onset nystagmus), including infantile nystagmus syndrome (INS), fusion maldevelopment nystagmus syndrome (FMNS) or spasmus nutans. Acquired nystagmus on the other hand, rises later in life.

Sarvananthan et al. (2009) conducted a study of nystagmus in Leicestershire in 2003 and found a prevalence of 24.0 in 10,000 in the general population. In those less than 18 years old, nystagmus was estimated to have a prevalence of 16.6 per 10,000. In this younger group

of people, the most common form of nystagmus was INS associated with albinism (3.2 per 10,000 population). In contrast, the prevalence of nystagmus was found to be much higher in the adult population (26.5 per 10,000 population), with the most common form of nystagmus being associated with neurological problems (8.3 per 10,000 population). They also observed nystagmus in children with Down's syndrome (DS). However, the prevalence of nystagmus in this group of children was not determined. Nonetheless, a number of other studies have found that the prevalence of nystagmus in children with DS was between 15-30% (Wagner, Caputo and Reynolds 1990; Averbuch-Heller et al. 1999; Kim et al. 2002). Interestingly, the prevalence was found to be quite variable in different parts of the world: 4.8% in Nigeria (Adio and Wajuihian 2012), 22% in South Korea (Kim et al. 2002) and 33.3% in Malaysia (Liza-Sharmini, Azlan and Zilfalil 2006). The presence of nystagmus can have a great impact on not only the visual function, but also the quality of life of a person who suffers from it (McLean, Windridge and Gottlob 2012).

Nystagmus waveforms can be generally characterised as either pendular or jerk (Neely and Sprunger 1999). The velocity of a pendular eye movement is equal in both directions. According to Scheiman and Wick (2008), the waveform of pendular nystagmus can change direction smoothly producing a sinusoidal waveform or it can change direction abruptly, producing a triangular waveform. Jerk movements, however, consist of a slow phase in one direction followed by a corrective saccade, known as a fast phase. It is further described by the direction of the fast phase, whether it is left, right, up and down. Nystagmus can further be characterised based on the axis plane, that is, horizontal, vertical and torsional. It can also be a combination of any of these, which results in a oblique or circular pattern (Neely and Sprunger 1999; Wong 2008). Conjugacy of the eyes is another typical characteristic; both eyes move together in the same direction with the same amplitude and frequency. Conjugate eye movements are often seen in infantile and fusion maldevelopment nystagmus syndrome. However, if the eyes move together in the same direction, but at different amplitude and

frequency, then the nystagmus is known as disconjugate. This type of eye movement is often seen in spasmus nutans (Wong 2008).

Nystagmus waveform represents the position of the eye over time, and can be described by the amplitude, frequency and the overall pattern or shape of oscillation. The components of a nystagmus waveform are illustrated in Figure 1.1. The nystagmus intensity is the nystagmus amplitude multiplied by the frequency (Hanson et al. 2006). However, the amplitude and intensity of nystagmus are only considered as "cosmetic measures" that do not represent the potential visual acuity associated with INS waveforms (Hertle and Dell'Osso 2013). The intensity of nystagmus waveform is not constant and can be influenced by a number of factors. Among these factors is the direction of gaze. The intensity of nystagmus can be at the minimum at certain position(s) known as the "null zone". It has been found that the null zone is within 10° of the primary position in 73% of nystagmats (Abadi and Bjerre 2002). Nystagmus intensity also usually reduces when the eyes are converging (Gradstein et al. 1998). Besides that, the state of attention and fatigue is also related to the intensity of nystagmus (Abadi and Dickinson 1986). Stress, for example, has been found to increase the intensity of nystagmus (Cham et al. 2008; Jones et al. 2013)

Foveation is a period when the eye movement is "relatively slower" for a short period of time when the object of regard coincides with the fovea (Scheiman and Wick 2008). Eye velocity during the foveation period should be less than 4º/s (Dell'osso et al. 1992; Bifulco et al. 2003). The eye position should also be within 0.5º-2º of the target (Dell'Osso et al. 1992; Bifulco et al. 2003; Wiggins et al. 2007; Jones et al. 2013).

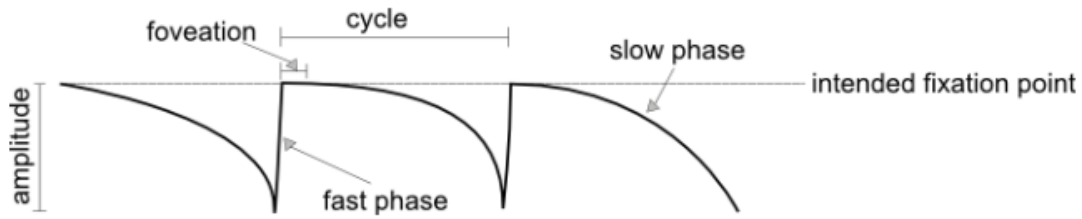

Figure 1.1 Illustration of nystagmus waveform components (IN-Vision 2015)

1.2.2 Types of nystagmus

Nystagmus can be classified into three different categories: physiological nystagmus, early onset nystagmus and acquired nystagmus (Ehrt 2012).

1.2.2.1 Physiological

In the previous section, nystagmus was described as an abnormality of eye movements. However, in addition to early onset and acquired forms, there is also physiological nystagmus, which is not abnormal. Physiological nystagmus refers to nystagmus that is seen in normal and healthy person. There are three forms of physiological nystagmus commonly seen: optokinetic nystagmus (OKN), vestibulo-ocular reflex (VOR) and end point nystagmus. These will be discussed briefly in the following section.

Optokinetic nystagmus (OKN)

OKN is a reflex of the eyes that is driven by retinal image motion, induced by rotation of the head or movement of the body or surroundings. The function of optokinetic eye movement is to keep the image of the world relatively steady on the retina during “constant head rotation” (Hertle and Dell’Osso 2013) or movement of the visual environment. Rotating a large striped drum in front of the unmoving subject can stimulate OKN. This will produce a slow phase smooth pursuit movement in the direction of the stripe which is then followed by a corrective saccade in the opposite direction (von Noorden and Campos 2002). Over time,

this will cause the subject to experience a “self-rotating” sensation known as “circularvection” (Leigh and Zee 2015; Wong 2008).

Vestibulo-oculo reflex (VOR)

VOR is an eye movement that allows the vision to be clear and stable by keeping the retinal image relatively steady during head movement. This is done by rotating the eyes in the opposite direction but at the same speed, as the head movement (Wong 2008). During head movement, two components take place: the angular (rotational) and linear (translational) component. These two components are sensed by different structures in the inner ear. The semi-circular canal senses the angular component whereas the otoliths organs sense the linear component, which then send signals to the VOR system (Leigh and Zee 2015). Vestibular nystagmus is interpreted by jerk movements of the eyes that occurs when the eye has reached the limit of its rotation.

End-point nystagmus (EPN)

End-point nystagmus occurs when the eyes are attempting to maintain fixation of an eccentric target. The cause of EPN is believed to be a deficiency in the *neural integrator network*. At eccentric gaze, the “leaky neural integrator” cannot hold the eyes at fixation steady and so they drift back towards the primary position. The drift is then followed by a corrective saccade to move the eyes back to the eccentric position, and the process is repeated producing a nystagmus (Hertle and Dell’Osso 2013). Eizenman et al. (1990) explained that EPN could be divided into three different categories, which are sustained EPN, unsustained EPN and fatigue EPN. EPN usually dampens after a few seconds. However, if the nystagmus is sustained after the eyes return to the central position, it is considered pathological and is known as “gaze-evoked nystagmus” (Leigh and Zee 2015). “Rebound nystagmus” is another type of nystagmus that occurs after a period of eccentric gaze holding.

1.2.2.2 Acquired nystagmus

Nystagmus that occurs at any point in life due to a disease or an injury is referred to as acquired nystagmus. The symptom that is usually associated with acquired nystagmus is oscillopsia, which is a perception that the environment is moving to-and-fro (Tilikete and Vighetto 2011; Ehrt 2012). Acquired nystagmus may be caused by visual system disorders that affect gaze stability, vestibular imbalance or disturbance of the steady eccentric gaze mechanism (Stahl, Averbuch-Heller and Leigh 2000). The most common diseases that are associated with acquired nystagmus are multiple sclerosis and stroke (Choudhuri, Sarvananthan and Gottlob 2007). Acquired nystagmus can present in both adults and children, although it is more frequent in adults with (40%) than children (17%) with nystagmus (Sarvananthan et al. 2009).

1.2.2.3 Early onset nystagmus

Nystagmus that occurs in the first few months of life and is not caused by any diseases or injuries is described as early onset nystagmus. As described in section 1.2.1, the three most common forms are fusion maldevelopment nystagmus syndrome (FMNS), infantile nystagmus syndrome (INS) and Spasmus Nutans syndrome (SNS). The characteristics of each of these types are further discussed in the sections below, focusing primarily on FMNS and INS.

Fusion Maldevelopment Nystagmus Syndrome (FMNS)

FMNS can be described as horizontal jerk nystagmus that becomes more apparent when one eye is occluded. It is usually associated with “uniocular neonatal visual defects” such as infantile esotropia. FMNS (also known as latent/manifest latent nystagmus, LMLN) usually has an early onset and cannot be acquired later in life. Infants can also exhibit both components of infantile and latent nystagmus (Harris 2013). FMNS is the most common form of nystagmus that in childhood (Ehrt 2012).

FMNS can present in two forms. The first form, a rare condition, is known as true/pure latent nystagmus (LN) (Dell'Osso, Schmidt and Daroff 1979; Abadi and Scallan 2000; Hertle 2017), with a prevalence of LN reported to be 1:16,000 (Sarvananthan et al. 2009). According to Harris (2013), LN does not present under binocular viewing. However, when one eye is occluded, bilateral conjugate, jerk nystagmus that is predominantly horizontal is observed. The velocity of LN slow phases is either linear or decreasing. The fast phase of LN beats towards the fixating eye. The intensity of LN increases when the eye is abducting and decreases (at times even disappearing) on adduction. LN is believed to be associated with strabismus, primarily esotropia which, develops in 1% of the general population (Major et al. 2007). Almost half of this population presents with LN. A schematic illustration of a LN waveform is illustrated in Figure 1.2.

The second form of FMNS is known as manifest latent nystagmus (MLN). MLN is also a jerk, horizontal nystagmus that is present under binocular viewing, hence the term manifest, but may not be detected clinically as the intensity is very small. However, the intensity becomes larger as one eye is occluded. As in LN, the fast phase of MLN also beats towards the fixating or the uncovered eye. In patients with alternating esotropia, the fast phase changes depending on the fixating eye. MLN components are often mixed with the components typical of IN, producing a complex waveform. MLN is often associated with patients with Down's syndrome (Papageorgiou, McLean and Gottlob 2014).

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Figure 1.2 Schematic of latent nystagmus showing eye position plotted against time (Harris 2013)

Abadi and Scallan (2000) studied the waveform characteristics of 37 patients with MLN between the ages of 18 to 67 years old. They were able to categorize MLN into 4 distinct forms based on the waveforms observed with both eyes viewing. In the first form (Type 1), the patient exhibits stable fixation. This type of MLN is actually referred to as latent nystagmus, which has been described above (Harris 2013), but this type is rare. The second form of MLN (Type 2) was described as conjugate horizontal square-wave jerks and is also uncommon. The third type (Type 3) was the most common type of MLN observed, and was described as a conjugate torsional nystagmus. The fourth type of MLN (Type 4) was described as a conjugate horizontal latent nystagmus that is present when both eyes are open. The slow phase of Type 4 MLN can either be decelerating or linear during both binocular and monocular viewing. Illustrations of all four types of MLN are shown in Figure 1.3.

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Figure 1.3 Illustration of the four types of MLN waveforms (Abadi and Scallan 2000)

The intensity of FMNS varies in different gaze angles. On adduction, the intensity is minimal, causing an "adduction null" in the fixating eye. This null position, however, is not considered as a "true null". Nonetheless, patients with FMNS change their fixating eye so that it is always the adducting eye. In order to place the fixating eye in adduction, the patients will rotate their head in the opposite direction of the target in view (Hertle and Dell'Osso 2013). Patients with FMNS also acquire dissociated vertical deviation (DVD) to dampen the FMN. This was observed by Guyton et al. (1998) in 10 patients with DVD and FMNS using scleral search coil eye movement recording. Initially, the nystagmus was present with one eye occluded, but dampened when DVD was developed with head tilt.

Infantile nystagmus syndrome (INS)

Infantile nystagmus (IN) is characterised by a conjugate involuntary eye movement that is typically horizontal and occurs within 6 months after birth. It is also known as infantile nystagmus syndrome (INS) and was formerly referred to as congenital nystagmus (CN). An earlier study by Reinecke et al. (1988, as cited by Gottlob 1997) discovered that nystagmus developed in the first 2 weeks of life in three of the 35 subjects that were seen. Gottlob (1997) did not observe any presence of nystagmus at 5 weeks after birth in a healthy full-term infant who was part of a vision development study, but the presence of nystagmus was observed pre-clinically at 7 weeks after birth and clinically at 8 weeks. Thus, it is difficult to specify a typical or more common age of onset for IN.

The classic classification of IN waveform was described in detail by Dell'Osso and Daroff in 1975. According to the authors, IN waveforms consists of three main categories, which are pendular, jerk and dual jerk. The pendular waveforms consist of pure pendular, asymmetric pendular and pendular with foveating saccades. Pendular nystagmus is illustrated in Figure 1.4. The jerk waveforms are divided into two sub-categories. The first two of these sub-types have saccadic foveation; pure jerk and extended foveation. The next two sub-types of the unidirectional jerk waveforms have slow eye movement (SEM); pseudo cycloid and pseudo jerk. These four waveforms are illustrated in Figure 1.5. The second type of jerk nystagmus is bidirectional (Figure 1.6) and is further divided into four sub-types; pure pseudo pendular, pseudo pendular with foveating saccades, triangular and bidirectional jerk (see Figure 1.7). The characteristics of this component are a pendular oscillation with variable amplitude and high frequency that is superimposed on a jerk nystagmus with higher amplitude. Therefore, there are 12 types of IN waveforms in total.

a. Pure pendular b. Asymmetric pendular c. Pendular with foveating saccades

Figure 1.4 Three types of pendular nystagmus (Hertle and Dell'Osso 2013)

a. Pure saccadic foveation b. Extended saccadic foveation

c. Pseudo cycloid SEM foveation d. Pseudo jerk

Figure 1.5 Unidirectional jerk nystagmus (Hertle and Dell'Osso 2013)

a. Pure pseudo pendular b. Pseudo pendular with foveating saccade

c. Triangular d. Bidirectional jerk

Figure 1.6 Illustration of bidirectional jerk (Hertle and Dell'Osso 2013)

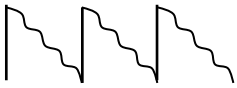


Figure 1.7 Illustration of dual jerk nystagmus (Hertle and Dell'Osso 2013)

Another approach to classify INS waveforms was developed by Harris et al. (2012), which they called the "adaptationist approach". This approach was based on plastic period of the oculomotor development, which is adaptive in nature. Due to this nature, the infant oculomotor system adapts within its limits to the visual environment. However, extremities that occur in the visual environment may cause a unique development in oculomotor system, such as nystagmus (Harris 2011). The adaptationist method of classifying nystagmus waveform classifies the nystagmus waveform into two classes: type 1 and type 2. The two classes are determined by examining the velocity profile of the nystagmus waveform. Type 1 nystagmus is associated with underlying velocity drive with normal downstream control, whereas type 2 waveforms are associated with either anomalous neural integrator or saccadic system with no oscillatory drive. The two types of waveform from the adaptationist method implies that the "cortical input, possibly from area V5, can modify the neural integrator" (Harris, Waddington and Erichsen 2012).

The development of IN waveform has been studied by a number of researchers. One of the earliest studies was by Reinecke et al. (1988) who reported that IN started with large triangular waveforms, developing into pendular and subsequently jerks waveform nystagmus in three infants. However, in a later study, Gottlob (1997) observed square-wave jerks at 7 weeks of age, which then developed into a smaller amplitude pendular nystagmus at 8 weeks in a healthy infant. The nystagmus then further became a large amplitude right and left beating nystagmus, which was seen at 10 weeks, and the amplitude had increased further (30°) at 11 weeks. At 14 weeks, the nystagmus became predominantly pendular, with a smaller amplitude (between 10-20°). The amplitude reduced even more at 6.5 and 7.5

months. A more recent study was conducted by Theodorou et al. (2015) on a group of 20 infants aged between 4 to 42 months in whose nystagmus they observed a combination of two components, i.e asymmetric pendular and pseudocycloid waveforms, which were different to anything observed by previous studies. Another difference observed was the decrease in the amplitude of both components of waveforms from birth until 1.5 years old. Foveation duration also improved up until the age of 1.5 to 2 years and remained stable after that.

IN can occur together with visual system disorders such as albinism, cataract, achromatopsia, corneal opacities and many more (Leigh and Zee 2015). However, it can also present without any associated visual sensory or neurological deficit and is therefore known as Idiopathic Infantile Nystagmus (IIN) (Neely and Sprunger 1999). Typically, IN is described as comprising a conjugate eye movement in the horizontal plane, although torsional components may be also be present (Leigh and Zee 2015). IIN has been shown to be caused by mutation of the *four point one ezrin, radixin, moesin domain-containing 7* (*FRMD7*) gene, first discovered in 2006, which can be inherited as an X-linked trait (Tarpey et al. 2006). 28 mutations of this gene have been documented until 2007 (Self and Lotery 2007) and further mutations have been discovered in Asian families since then (Li et al. 2012; Liu et al. 2013; Radhakrishna et al. 2012; Xiao et al. 2012). More recently, mutation of the *PAX-6* gene was discovered in IIN which is autosomal-dominant in nature (Thomas et al. 2014).

Spasmus Nutans Syndrome (SNS)

SNS is a combination of nystagmus, head nodding and abnormal head posture (head turn or head tilt). The onset of SNS is usually in the first year of life, between 4 and 18 months (Scheiman and Wick 2008; Hertle and Dell'Osso 1999), and will usually disappear after 2 years. However, SNS can occasionally last up to 8 years or persist with an intensity that is reduced to a subclinical level. Nystagmus in SNS is mostly bilateral, although it may be different in each

eye and can even appear monocularly (Hertle and Dell'Osso 2013). It oscillates predominantly in the horizontal plane but can sometimes have vertical or torsional components. The form of nystagmus is intermittent pendular with small amplitude and a frequency between 3-11Hz. The intensity of the nystagmus is higher in the abducting eye and, in contrast to IN, will increase during convergence (Wong 2008).

1.2.3 Quantifying nystagmus

Many methods have been developed to quantify nystagmus to track changes in the nystagmus function, such as the *nystagmus acuity function* (NAF)(Sheth et al. 1995) nystagmus acuity estimator function (NAEF)(Cesarelli et al. 2000), expanded nystagmus acuity function (NAFX) (Dell'Osso and Jacobs 2002), automated nystagmus acuity function (ANAF)(Tai et al. 2011) and nystagmus optimal fixation function (NOFF)(Felius et al. 2011). The quality of the foveations and intensity are considered in every method mentioned above.

The NOFF method has been claimed to be the most suitable method to quantify nystagmus in children. As children can be easily distracted, eye movement recording data in children are often noisy, with a lot of missing data. The NOFF algorithm was designed taking into account head and body movement that often occurs during eye movement recordings with children (Felius et al. 2011). The algorithm looked for foveation periods in a 4-second window containing the cleanest eye movement data. Foveation was defined as periods of where the eye velocity was at the lowest and the eye positions were nearest to the target position (Dell'Osso and Jacobs 2002). Fractions of the data meeting the foveation criteria, known as foveation fractions, were then used to calculate the NOFF values (described in logits) using the following formula:

$$NOFF = \log\left(\frac{foveation\ fraction}{1 - foveation\ fraction}\right)$$

The NOFF values ranged from approximately +5 logits to -5 logits. Greater the NOFF values relate to greater foveation fractions. NOFF values of zero indicate a foveation fraction of 0.5. Low values of foveation fraction (therefore low NOFF values) were shown to correlate with "larger age-corrected visual acuity deficits" (Felius et al. 2011).

1.3 Fixation and smooth pursuit in nystagmus

All of the different types of eye movements have a common purpose, which is to place and keep the image of an object on the fovea. The human retina has a very high spatial resolution in the foveal region (within 0.5° at the centre) and a lower spatial resolution at the periphery. Therefore, an image must be held steady on the fovea in order to achieve good vision. Eye movements are used to achieve this goal and can be categorised into two functional classes. The first class of eye movements, which consist of visual fixation, vestibular (VOR) and optokinetic (OKN) systems (Holmqvist et al. 2011), functions to hold the image of the object of regard on the fovea. The second class of eye movements, which consist of saccades, smooth pursuit and vergence, functions to move the image onto the fovea (Leigh and Zee 2015). VOR and OKN have been discussed previously in section 1.2.2.1. The following sections will focus on visual fixation and smooth pursuit as well as the characteristics of each eye movement in nystagmus.

1.3.1 Fixation

The visual fixation system functions to hold the image of the viewed object stationary on the fovea. Although the image is kept steady on the fovea, the eyes are not *completely* stable. The fixation system consists of three distinct types of small movements: microsaccades, drifts and tremor (Holmqvist et al. 2011). Microsaccades are small saccades with an amplitude of less than one third of a degree (Leigh and Zee 2015) with a mean frequency of about 120Hz (Wong 2008). Drifts or microdrifts are slow phase eye movements that function to prevent the image of an object from fading (Wong 2008). The velocity of a microdrift is often less than

20 min of arc per second. Finally, the tremor is an eye movement of high frequency (50-100Hz) with amplitudes of less than 1 minute of arc.

The eyes are constantly moving in individuals with nystagmus, with the slow phase drifting the eyes away from the object of regard, followed immediately by the fast phase that redirects the eyes back to the object. Therefore, it can be said that the behaviour of fixational eye movement in nystagmats is not typical. Previous studies looking at eye movement during fixation in adults with nystagmus focused on determining the slow phase properties (Abadi and Worfolk 1989), foveation criteria (Chung and Bedell 1996), or the location of the null zone (Dell'Osso 1973; Abadi and Whittle 1991), Similarly, in children with nystagmus (with and without DS) fixation studies have mostly focused on waveform classification (Theodorou et al. 2015; Weiss, Kelly and Phillips 2016) or foveation criteria (Felius et al. 2011; Felius and Muhanna 2013; Felius, Beauchamp and Stager 2014).

Only recently, Kelly, Phillips and Weiss (2018) investigated whether eye velocity affects the normal development of VA in children with IN. The study involved 15 children with IN who were 6 years old or younger. Eye velocities that would limit VA was predicted using the following formula:

$$log\ velocity\ (age) = \frac{logMAR(age) - intercept}{slope}$$

(Kelly, Phillips and Weiss 2018)

LogMAR(age) is the age adjusted VA obtained from published norm. The intercept and slope values were from previous adult studies that showed a strong relationship between retinal image motion and VA (Demer and Amjadi 1993; Tai et al. 2011). Kelly, Phillips and Weiss (2018) showed that the eye velocities of typically developing children with IN were below the limit that would reduce visual acuity, at least 4% of the time. Therefore, the authors

hypothesized that decreased visual acuity during visual development in these group of children may be caused by “increased visual system noise” and “imprecise foveation” (Kelly, Phillips and Weiss 2018).

1.3.2 Smooth pursuit

Smooth pursuit comprises a slow phase conjugate eye movement that tracks a slow moving target to maintain its image on the fovea. The main functions of smooth pursuit is: 1) to stabilize to image of the moving target on the fovea; 2) to cancel the VOR so that the eyes move in the direction of the intended gaze; and 3) to cancel the OKN to a detailed stationary background over which the target moves (Wong 2008). The characteristics of smooth pursuit are described in terms of velocity, latency and gain. The normal velocity of smooth pursuit ranges between 0.1°/s to 70°/s. The latency period is shorter than that of saccades (between 100 to 130ms). Smooth pursuit velocity gain is determined by dividing the mean eye velocity by the mean target velocity. Gain values that are near 1.0 imply that the eye movement is matching the target movement. A normative study of eye movements in typically developing children by Vinuela-Navarro (2015) reported the smooth pursuit velocity gain ranging from 0.84 to 0.94 for children between the age of 4 to 11 years old for targets moving at 6º/s.

Smooth pursuit occurs in two phases. The first phase is the initiation of the smooth pursuit, known as the open loop phase. During this phase, there is an initial acceleration, which occurs within the first 20 to 40ms. This initial acceleration does not depend on the target velocity. Following this, the acceleration of the smooth pursuit depends on the target velocity. The second phase of a smooth pursuit is the “steady state”, also known as the closed loop phase, which occurs after the latency period. During this phase, the extra-retinal feedback of eye velocity from the brain is added to the retinal slip velocity in order to determine the target velocity. This functions to maintain the pursuit (Leigh and Zee 2015). A known characteristic of a pursuit is that it will show a phase lag of about one latency period behind the target when

tracking an unpredictable moving target. However, when a predictable moving target is tracked, there is no phase lag (Wong 2008).

1.3.2.1 Development of smooth pursuit

An early study suggested that smooth pursuit eye movements are not present in early life and that tracking in infants consists of a sequence of saccades (Dayton et al. 1964). However, later studies disagreed with these findings and suggested that smooth pursuit eye movements are present in early infancy (Kremenitzer et al. 1979; Roucoux, Culee and Roucoux 1983; Shea and Aslin 1990). A study by Lengyel et al. (1998) found that infants were able to perform short segments of smooth pursuit as young as one day old. However, the smooth pursuit gains and pure smooth pursuit segment for very young infants are found to be low. The total smooth pursuit time increases with age and is thought to be due to an increase in attention. A study by Phillips et al. (1997) observed similar findings in infants aged 1 to 4 months old. However, the presence of smooth pursuits in infancy can be affected by the characteristics of the stimulus in terms of both size and velocity (Shea and Aslin 1990; Hofsten and Rosander 1997). Smooth pursuit gain have previously been shown to remain immature throughout childhood and reaches adult values during adolescence (Katsanis, Iacono and Harris 1998; Salman et al. 2006). However, a more recent study by Vinuela-Navarro (2015) showed that smooth pursuit gains are adult-like from 7 years old when child-friendly stimuli were used to record the eye movements, with gains ranging from 0.84 to 0.94.

1.3.2.2 Smooth pursuit in nystagmus

Very little is known of eye movement performance in children with nystagmus when they pursue a moving target. To the best of the author's knowledge, the only study on smooth pursuit performance involving children with nystagmus was conducted by Weiss et al. (2016) on children with DS. This study will be discussed further in section 1.5.2.3. Other studies of smooth pursuit in IN have largely been conducted on adults (Dell'osso 1986; Jacobs and

Dell'Osso 2004; Brodsky and Dell'Osso 2014; Dell'Osso and Jacobs 2013; McIlreavy 2016). Early studies of pursuit in adults with IN found lower pursuit gain in adults with IN compared to those without IN (Yee, Baloh and Honrubia 1980; Yamazaki 1978). In these studies, the entire nystagmus slow phase was used to calculate the gain. However, it has been argued that the entire slow phase should not be used to determine gain in IN, as it is present even during fixation (Dell'Osso 1986). Therefore, in later studies of pursuit in, gain was calculated using the foveation periods in the nystagmus waveform (Jacobs and Dell'Osso 2004; Brodsky and Dell'Osso

Although there were differences in the methods used in the early and later studies of pursuit in IN were, all of the studies used one common measure to determine the pursuit performance, which was gain. However, there are limitations to using this approach as pointed out by McIlreavy (2016). First, gain restricts the assessment of the eye movement performance to only one visual axis at a time. Second, gain cannot be used to calculate fixation and therefore, the performance of during pursuit and fixation cannot be compared.

To overcome these limitations, McIlreavy (2016) conducted a study assessing the accuracy and precision of eye movements in adults with IN when following a target that moves horizontally and vertically at different target frequencies (0.5Hz, 1Hz and 2Hz). In general, his findings showed that adults with IN have poorer accuracy and precision than controls when following a moving target. Accuracy reduced as the target frequency increased. In contrast, precision increased with increasing target frequency.

1.4 Visual functions in nystagmus

1.4.1 Visual acuity

A study by Abadi and Bjerre (2002) looked at motor and sensory characteristics of infantile nystagmus. The authors discovered that there was a reduction in the visual acuity of adults with INS, with the mean VA of 0.35 logMAR in the idiopaths, 0.67 logMAR in the albinism group, and 0.55 logMAR in the group with ocular anomaly. This decrease in VA was suggested to be the result of the inability to maintain stable foveal vision, producing retinal image motion (Chung and Bedell 1995; Chung and Bedell 1996). A minimum of 2°/sec of retinal image motion can reduce visual acuity in normal adults (Westheimer and McKee 1975; Weiss and Kelly 2007).

Dunn et al. (2014) argued that image motion was not the factor that limits VA in nystagmats specifically those who were idiopathic. The authors measured grating VA on adults with idiopathic infantile nystagmus under tachitoscopic and constant illumination. Tachitoscopic illumination was achieved using a flash unit aimed reduce motion blur in an imaging system, a technique widely used in photography. Therefore, VA in nystagmats was expected to improve under this lighting condition. Interestingly, the authors did not find any significant difference in the VA between the two lighting conditions. They suggested that the VA limitation may be due to "underlying pathology or stimulus deprived amblyopia that may have resulted from motion blur during the critical period of visual development"(Dunn et al. 2014). At birth, visual acuity in typical children is immature, and then improves rapidly from 1 to 6 cycle/degree between the ages of 1 to 6 months (Teller et al. 1986; Preston et al. 1987). Therefore, infants with nystagmus might be expected to be more tolerant to retinal image motion due to this low acuity.

The development of visual acuity in children with INS has been studied by many researchers (Weiss and Kelly 2007; Fu et al. 2011; Felius et al. 2011). According to Weiss and Kelly (2007),

the development of visual acuity in children with INS parallels normal acuity development, regardless of its association with sensory disorders. The authors suggested that reduced acuity in subjects with IN and associated sensory disorders were predominantly limited by the macular hypoplasia or optic nerve dysfunction. Fu et al. (2011) suggested that the pattern of visual acuity development in children with INS depends on the presence or absence of the sensory system deficits.

There is limited literature on the development of visual acuity in those with FMNS. Individuals with FMNS can have worse vision under monocular viewing as compared to binocular, as the nystagmus appears when one eye is covered. However, some patients may have "accurate foveation" under both conditions, therefore maintaining their visual acuity (Hertle and Dell'Osso 2013). Good visual acuity in patients with INS is related to the long "postsaccadic foveation periods" in the waveforms of INS. However, such periods are not present in FMNS waveforms. Instead, FMNS patients were discovered to have a dual foveation strategy (Dell'Osso et al. 1995, as cited by Hertle and Dell'Osso 2013).

1.4.2 Contrast sensitivity

In children with normal vision, contrast sensitivity is present in early infancy and improves until the age of 7 years old (Beazley et al. 1980; Adams and Courage 2002; Leat, Yadav and Irving 2009; Almoqbel, Irving and Leat 2017). Individuals with nystagmus have reduced contrast sensitivity for medium to high spatial frequency vision with a higher threshold for pattern detection. This impairs the patient's ability to detect vertically oriented stationary and moving targets more than horizontal ones (Hertle and Dell'Osso 2013). A study by Bedell (2006) showed that contrast sensitivity in some subjects with nystagmus is worse than that of normal subjects.

1.4.3 Stereopsis

The presence or absence of stereopsis is a measure of state of binocularity in a subject. Studies have shown that stereopsis only first appears after the age of 3 months old, rapidly developing by the age of 6 months. The measurement of stereopsis in nystagmus patients can be obtained if they have good binocularity. A study by Liu and Yang (1997) measured stereopsis in 57 patients with INS, of whom only 8 had normal stereopsis (all had jerk nystagmus). The authors also discovered that most of the patients with pendular waveforms and more than half of those with jerk waveforms had impaired stereopsis. They also discovered a relationship between acuity and stereopsis; the better the acuity the lower the impairment of the stereopsis.

1.5 Nystagmus in Down's syndrome

Down's syndrome (DS) is a genetic disorder resulting from an extra copy of all or part of chromosome 21. The extra genetic material disrupts the normal developmental processes, leading to intellectual, medical and physical abnormalities in individuals with DS. In England and Wales, the estimated prevalence of 6.6 in 10,000 people had DS in 2011 (Wu and Morris 2013).

Children with DS present with a few common physical characteristics, which, were first described by John Langdon Down in 1866 (Creavin and Brown 2009). These physical characteristics are upward slanting of the palpebral fissure with epicanthal fold, underdeveloped nose bridge, protruding tongue, and short hands (Barnard and Edgar 1996). They also present with significantly more ocular manifestations as compared to the normal population. Some of the most common ocular disorders are significant refractive errors (myopia, hyperopia and astigmatism), accommodative insufficiency, strabismus, congenital cataract, and keratoconus (Creavin and Brown 2009).

Nystagmus is also one of the most frequently seen ocular disorders in children with Down's syndrome. It was estimated to occur in 15-30% of individuals with DS (Wagner, Caputo and Reynolds 1990; Averbuch-Heller et al. 1999). However, recent studies have shown a wider range of prevalence of nystagmus among individuals with DS. Adio and Wajuihian (2012) found that only 4.8% of children with DS in Nigeria presented with nystagmus. Prevalence of nystagmus among children with DS in the UK was found to be 16% (Stephen et al. 2007). A much higher percentage of nystagmus was observed among individuals with DS in Asia. Kim et al. (2002) and Paudel et al. (2010) found 22% and 28% of children with DS had nystagmus in Korea and Nepal, respectively. The highest prevalence (33.3%) was seen among Malaysian children with Down's syndrome in a study by Liza-Sharmini et al. (2006). Although there is a frequent occurrence of nystagmus in children with DS, there are very few studies conducted to investigate the development of nystagmus in these children, i.e. whether it develops in the same way as it does in typically developing children. Furthermore, the accuracy of eye movements in children with nystagmus and DS has yet to be studied.

Another factor that has been found to be associated with nystagmus and DS is congenital heart disease. It is estimated that 44% of children with DS are born with congenital heart disease (Freeman et al. 1998). A relationship between congenital heart defect and nystagmus in DS has been observed (Bromham et al. 2002). In that particular study, 9 out of 11 children with DS between the ages of 1 to 9 years old with a heart defect presented with nystagmus. It is therefore expected that children with DS and heart defects have a higher risk of developing nystagmus in the first 9 years of their life as compared to those who did not have any heart defects. A separate study by Kranjc (2012) also found a significant relationship between heart defects and nystagmus in children with DS. In contrast, a study by Ljubic et al. (2015) did not observe any significant increase in the occurrence of nystagmus between individuals with DS who did and did not have heart defects. The study, which was conducted on children and young adults with DS between 5 and 22 years of age, only observed the presence of nystagmus in 2 out of 54 subjects (1.9%) with congenital heart defects. A higher

percentage of nystagmus (2.6%) was seen in the control group of children with DS who do not have heart defects. The type of nystagmus, however, was not recorded in either study.

1.5.1 Characteristics of nystagmus in DS

One of the earliest classifications of nystagmus in DS was done by (Wagner, Caputo and Reynolds 1990). They conducted a study on 188 children and adults with DS between the ages of 4 months to 24 years and discovered that 56 (29.8%) of them had nystagmus. They were able to clinically distinguish the nystagmus into four groups. The first group was described to be horizontal and asymmetric with high frequency and very small amplitude. The nystagmus was observed to be different at each gaze angle and appeared to be pendular. However, the rapid speed made it difficult for the author to confirm the actual waveform. The characteristic of the second group was similar to that of the first group but was symmetrical clinically. Group 3 had noticeable nystagmus only when one eye was occluded. The movement of the nystagmus were found to be fine and rapid and therefore was classified as either latent or manifest latent nystagmus. The authors noted that these three groups of nystagmus had some features of spasmus nutans in which they described the eye movements as “shimmery, quivery or jiggle”. These features are not normally seen in typical congenital nystagmus. The final group of nystagmus was described to be “course conjugate jerk nystagmus.” The authors also noted a difference in the mean age of the patients for each group of nystagmus. Groups 1 and 2, which had similar characteristics, were observed in younger patients (mean ages 4.4 and 2.2, respectively). Groups 3 and 4 were observed in the older group of patients (mean age 7.8 and 17 years, respectively).

The classification of nystagmus in DS by Wagner, Caputo and Reynolds (1990) was based on clinical observation. However, eye movement recording is a much more accurate way to look at nystagmus in DS as it can provide a quantitative description of the nystagmus waveform in terms of amplitude, frequency, foveation and direction, allowing us to classify the type of

nystagmus better. The earliest investigation of nystagmus in adults with DS using eye movement recording was performed by Averbuch-Heller et al. (1999). The recording was performed on 26 adults and one 3 years old child with DS using an infrared reflection method. Fixation, saccades, smooth pursuits, near viewing and effects of darkness were examined. The authors discovered that 6 (23%) of the adults with DS exhibited Latent/Manifest Latent Nystagmus (LMLN) waveform. A combination of congenital nystagmus and LMLN waveform was observed in the child with DS. Disconjugate movement resembling that of spasmus nutans was sometimes noticed, similar to the findings of (Wagner, Caputo and Reynolds 1990) in this same age group of children with DS.

One of the earliest studies of eye movement recording on children with DSN was by Felius et al. (2014). The study involved 16 children with DSN between the age of 10 months to 14 years old using the Eyelink 1000. Simple fixation tasks were carried out for 20 to 30 seconds with both eyes open. Results from this study showed the waveform characteristics of IN in 14 (87.5%) of the children involved. The remaining two children presented with waveform patterns of MLN; aged 3.4 and 3.7 years, i.e. much younger than the mean age of the children with DSN observed in Wagner, Caputo and Reynolds (1990)'s third group of children. These findings were different from that reported in a more recent study by Oladiwura, Shweikh and Theodorou (2018), who reported a much lower prevalence of IN (8.33%) and FMNS (6.25%) in their study involving 48 children with DSN. However, a very high occurrence (83.33%) of "manifest horizontal nystagmus" was reported (Oladiwura, Shweikh and Theodorou 2018), although, the characteristics of this type of nystagmus was not explained. The same study also reported a 2.08% occurrence of Internucelar Ophthalmoplegia in their group of children with DSN. Both studies by Felius et al. (2014) and Oladiwura, Shweikh and Theodorou (2018) did not report any component that resembles the features of spasmus nutans in this group of participants. Neither of the studies reported detailed characteristics of the IN waveform.

To date, the most detailed characterisation of nystagmus in children with DSN was by Weiss, Kelly and Phillips in 2016. They reported an occurrence of one to four waveform types in each of their 17 children with DSN presenting with IN type of waveforms (age range 0.4 to 16.9 years). The waveform types were either jerk, constant velocity slow phase, horizontal pendular, vertical pendular and square-wave jerk. The amplitudes and frequencies of the nystagmus ranged from 3º to 12º and 2Hz to 7Hz respectively. Combinations of multiple nystagmus waveforms were frequently observed in children younger than 1.6 years old.

Based on the literature discussed above, there seems to be a difference in the type of nystagmus seen between children and adults with DS. This implies that the waveforms in children with DS may change over time as the child grows, although it is not certain when and why these changes happen and if the changes are the same as seen in typical developing children with nystagmus. The studies discussed above also only analysed horizontal eye movement data. Although INS is characterised as being predominantly horizontal, oscillation on the vertical axis may occur (Abadi and Bjerre 2002). Therefore, in the present study, we examined both horizontal and vertical eye movement data.

1.5.2 Visual function in children with nystagmus and DS

1.5.2.1 Distance visual acuity

Visual acuity (VA) in children with DS who are older than 2 years old has been noted to be lower than that of the typically developing children (Woodhouse et al. 1996). This could be caused by ocular disorders that occur in this group of children, such as strabismus, high refractive error, nystagmus or even a combination of causes (Tsiaras et al. 1999). A recent retrospective study by (Zahidi, Vinuela-Navarro and Woodhouse 2018) compared the binocular visual acuity (BVA) of 159 children with DS to published norms. The study reported that the BVA of children with DS starts to stabilise from four years old with the VA of approximately 0.25 logMAR.

Most studies of VA in children with DS often exclude children with nystagmus from their analysis (Little et al. 2007; Little et al. 2009; Tomita 2017; Zahidi et al. 2018). Therefore, very little is known regarding the visual performance of this group of children. To date, one study has investigated the visual acuity deficit of children with DS and nystagmus (DSN)(Felius et al. 2014). The study involved 16 children with DSN between the age of 10 months and 14 years old. Binocular VA was measured using forced-choice preferential looking method or pointing with the Teller card. VA deficit was defined as "the logMAR units relative to published aged-corrected mean normal values" (Felius et al. 2014). The authors discovered that the mean VA deficit of children with DSN was four lines poorer (0.4 logMAR) than the age-corrected mean. Despite the larger deficit (1.5 lines) than that of typically developing children with IN, the visual acuity deficit in children with DSN was considered mild. NOFF values were also determined from eye movement recording data and were found to be similar to that of typically developing children reported in an earlier study by the same research group (Felius and Muhanna 2013). Therefore Felius et al. (2014) suggested that nystagmus contributed to the all of VA deficit of children with DSN except for the 1.5 lines.

1.5.2.2 Near acuity

Near vision is important for children, as they like to look at objects at a close distance. In order to have clear near vision, three mechanisms take place, which are accommodation, convergence and constriction of the pupil (Von Noorden and Campos 2002). Near visual acuity has been reported to be better than distance visual acuity in patients with IN (Hanson et al. 2006). This is due to the dampening of the nystagmus during near work or convergence.

Reduced accommodation can result in poor vision at near. Children with DS are known to have a relatively poor accommodation as compared to typically developing children (Woodhouse et al. 1993; Woodhouse et al. 1996). Hence, it is expected that the near acuity

in this group of children is even poorer in the presence of nystagmus. However, there are no recent studies investigating the effect of nystagmus on near acuity in children with DS.

1.5.2.3 Fixational and smooth pursuit eye movements in children with DS and nystagmus

Studies of functional eye movement in children with DS are very limited. Two of the available studies of fixational eye movements in children with DSN were focused on characterising the nystagmus waveform types (Weiss, Kelly and Phillips 2016; Oladiwura, Shweikh and Theodorou 2018). The findings of these studies have been previously discussed in section 1.5.1. Another study, which was discussed in the previous section, looked at the characteristics of nystagmus waveform and investigated the relationship between fixation stability and its relationship to visual acuity deficits in this group of children (Felius, Beauchamp and Stager 2014). Children with DSN with IN type of waveform were reported to have similar NOFF values (-0.96 logits $\pm$ 1.7SD) to that of typically developing children with IN (-0.93 logits $\pm$ 2.1SD) with no significant difference, suggesting similar fixation stability in both groups of children.

Adults with DSN have been reported “asymmetric” smooth pursuit (Averbuch-Heller et al. 1999). To date, only one study investigated pursuit eye movements of 18 children with DSN (Weiss, Kelly and Phillips 2016). To evoke pursuit eye movement, the study used a “point” target that oscillated sinusoidally at an amplitude of 10º and the different constant velocities (10º/s, 20º/s and 30º/s). Apparent pursuit gain ranging between 0.3 to 0.4 was reported. From their findings, (Weiss, Kelly and Phillips 2016) concluded that children with DSN have “apparent pursuit” which was “superimposed on the slow phase of the nystagmus”.

1.6 Defining the accuracy and precision of fixation and smooth pursuit eye movements in children with nystagmus

Fixation and pursuit eye movements have the same goal, which is to maintain a stable image of the object on the fovea. However, the image is never perfectly still on the fovea in either task, producing a velocity error between the eye and the object image, known as retinal slip velocity. Since retinal slip velocities occur in both fixation and pursuit task, it is only logical to use this form of measure to compare the performance of both types of eye movements (McIlreavy 2016). Velocity gain is a common measure of retinal slip in pursuit task, derived by dividing the eye velocity by the target velocity (de Brouwer, Missal and Lefèvre 2001). However, the use of gain as a measure of eye movement performance only allows a one-dimensional analysis of the eye movement. For example, a horizontal moving target would have a velocity of 0º/s on the vertical axis. Therefore, the gain can only be calculated for the horizontal and not the vertical axis. Dividing the vertical eye velocity with the vertical target velocity of 0º/s would result in a gain of infinity. However, although it has been reported IN oscillations are predominantly horizontal (Abadi and Bjerre 2002), some individuals with IN do present with oscillation on the vertical axis suggesting that retinal slip velocities occur simultaneously on both horizontal and vertical axis. Therefore, using a one-dimensional analysis of the eye movement such as gain limits the ability to determine simultaneous imaging of the target on the fovea.

The measure of gain also cannot be implemented on fixation tasks, as the target is stationary (i.e. velocity = 0º/s); resulting in a gain of infinity. Hence, gain cannot be used as a measure of eye movement performance in fixation tasks, limiting comparisons between both types of eye movements. To overcome this issue, McIlreavy (2016) suggested an alternative method to quantify eye movement performance in fixation and pursuit tasks using a two-dimensional analysis which enable both the horizontal and vertical axis to be assessed simultaneously. The two-dimensional analysis enables the eye movement performance to be assessed in terms of accuracy and precision. Figure 1.8 illustrates the concept of accuracy and precision in a

schematic diagram. Accuracy refers to the closeness of a measured value is to a reference value. Precision can be described as the closeness of the measured values are to each other (variability). In terms of eye movement performance, accuracy would therefore refer to the eye velocity (mean measured value) required to match the target velocity (reference value). The variability of the eye velocities (i.e the standard deviation of the mean measured value). Precision provides information if the eye velocities are consistently matching the target velocity, hence imaging the target on the fovea at all times.

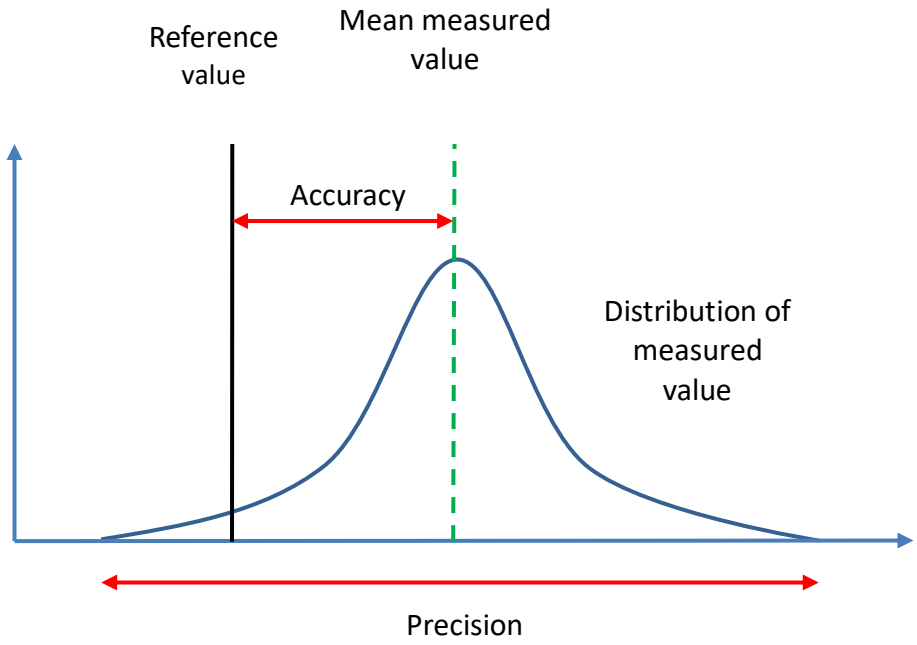


Figure 1.8 Schematic diagram illustrating the accuracy and precision. Accuracy is the closeness of the mean measured value (green dashed line) to the reference value (black line). Precision refers to the closeness of the measured value to each other (blue curved line)

1.7 Methods of eye movement recording

An eye tracker is a device used for measuring eye movements. According to Young and Sheena (1975), there are two techniques of eye movement recording in general. The first technique measures the position of the eyes relative to the head whereas the second measures the position of the eyes in space. There are four broad categories of eye movement recording. These are: scleral search coil, electro-oculography (EOG), photo-oculography (POG) and

video-based combined pupil (Duchowski 2007). Each of these categories will be discussed briefly in the following sections.

1.7.1 Scleral search coil

The scleral search coil is an eye movement recording method performed by placing a copper wire embedded silicon scleral lens on the anesthetised eye. An alternating (AC) current is passed through field coils surrounding the head creating an AC magnetic field. The position of the eye is determined by the amplitude of the current that is induced, which is detected by the coil. This method of eye movement recording is considered the gold standard of eye movement measurement due to the high spatial resolutions produced by the coil method that has low noise (Collewijn 1998). Nonetheless, this method has a major disadvantage due to its invasive nature. The lens causes discomfort to the subject even when the eye is anaesthetised (Collewijn 1998; Van Der Geest and Frens 2002). This limits the experiment time to a maximum of 30 minutes. Hence, this method may not be suitable for certain groups of subjects, especially children (Van Der Geest and Frens 2002). The use of scleral search coil in recording eye movements in nystagmus patients may also not be suitable. The presence of contact lens on the eyes dampens the nystagmus (Hertle and Dell'Osso 2013), which will affect the measurement of the subject's true nystagmus intensity.

1.7.2 Electro-oculography (EOG)

This method of eye movement measurement was discovered in 1922 by Schott and later by Mowrer and companions in 1936 (Young and Sheena 1975). The principle of this method is recording the corneoretinal potential differences by placing skin electrodes on the skin around the eyes. The corneoretinal potential is a difference in voltage between the cornea and retina, ranging from 15μV to 200μV (Duchowski 2007). The electrodes are placed on the outer canthi to measure horizontal eye movements. The advantage of using the EOG when recording eye movement is that it is a non-invasive method, therefore causing minimal

discomfort to the subject. Moreover, it can also record a large range of horizontal eye movement (±40°). The EOG has been widely used to study eye movements in children (Phillips et al. 1997; Hofsten and Rosander 1997) and also nystagmus (Lawson et al. 1996; Gottlob 1997). Nevertheless, there are limitations to using this method of eye movement recording, such as the fact that the electrodes pick up the presence of large muscle action potentials as potential differences, causing problems in linearity (Collewijn 1998). Apart from that, fluctuations in the corneoretinal potential causes variable calibration of the EOG, depending on the illumination level and the retina's state of light adaptation. Recording of vertical eye movements has also been found to be unreliable (Leigh and Zee 2015).

1.7.3 Photo-oculography (POG)

Also known as video-oculography (VOG), POG is a combination of eye movement recording techniques that involves measurements of certain features of the eyes such as pupil shape, limbus position, and corneal reflections of a directed light source (usually infrared). Two examples of POG eye movement systems are the Eyelink 1000 and the Tobii X300.

1.7.3.1 Eyelink 1000

The Eyelink 1000 (

Figure 1.9) is a remote eye tracker with a sampling rate of 1000Hz (monocularly) and 500Hz (binocularly). It has a spatial resolution of 0.1°, and is capable of tracking gaze angles up to 32° horizontally and 25° vertically. It allows head movements within a volume of of 25x25x10cm (width x vertical x depth) at a distance between 40cm to 70cm. However, the manufacturers (Research 2014) recommend the use of a chin rest when a spatial resolution is important.

Figure 1.9 Eyelink 1000 head mount and Eyelink 1000 core model with desktop mount

1.7.4 Tobii TX300

The Tobii TX300 (Figure 1.10) is another example of a remote eye tracker that uses infrared diodes to generate a corneal reflex, which is then detected by image sensors (Tobii Technology 2010). It has a sampling rate of 300Hz and consists of a large head movement box that allows the subject to move relatively freely at a distance of 65cm within a space of 37x17cm (width x height). Hence, no chinrest is necessary during eye movement recording. It can also track gaze angles up to ±35° with an accuracy of about ±0.4°. These features are a huge advantage in tracking eye movements in children and has been used successfully in previous study (Vinuela-Navarro 2015).

Figure 1.10 Tobii X300 (Tobii Technology 2010)

1.8 Summary and research objectives

Based on the literature survey discussed in this first chapter, it seems that the impact of nystagmus in children with DS on their visual acuity and eye movement performance has not yet been fully explored. Therefore, the current study was designed to answer the following questions:

a. Is the nystagmus in children with DS the same as typical children with nystagmus?
b. Does their nystagmus have a similar impact on the visual acuity of the two groups of children?
c. Is there a difference in the accuracy and precision during fixation and/or smooth pursuit in these two groups of children?

Therefore, to answer the above questions, the objectives of this study are to:

a. determine and compare the nystagmus waveforms and visual acuity between children with and without DS.
b. compare the accuracy and precision of eye movements during fixation and smooth pursuit between these two groups of children, as well as children with DS and typically developing children without nystagmus.

The overall goal was to determine the nature of nystagmus in children with DS as well as in typically developing children and its impact on their visual acuity and eye movement performance during fixation and pursuit. The hope was to provide clinicians, teachers, support services and even parents to a better understanding of the impact of nystagmus on the children with DS in order that they receive better informed support.

1.9 Thesis outline

The overall structure of the study takes the form of 8 chapters. This first chapter provided an overview of nystagmus and the impact of nystagmus on the visual function and eye movement. The second chapter of this thesis presents the findings of a retrospective analysis on the clinical data of the children with DSN that attended the Special Assessment clinic here at Cardiff University over the period of 20 years. The findings provide an insight to the visual acuity and refractive error development of children with DSN compared to those which has not been explored before.

Chapter 3 presents a description of the methods used in this study to achieve the aims of the research. This include details of the optometric tests and eye movement recording and data analysis procedures. This is followed by Chapter 4, where the child friendly laboratory set up for eye movement recording (EMR) on children is presented along with the experiments undertaken to determine the effect of the child friendly stimulus developed on nystagmus eye movement data. The challenges of eye movement recording on children faced and the steps taken to overcome the challenges during this study are also discussed. Chapter 5 then presents the development and validation of retrospective calibration method that will be used on the EMR data of the participants in this study is described.

The characteristics of the nystagmus waveform of children with and without DSN is presented in Chapter 6 followed by comparison of eye movement performance during fixation and smooth pursuit between children with nystagmus with and without DS and children without nystagmus with and without DS in Chapter 7. Finally, a summary of all experimental chapters is presented in Chapter 8.

CHAPTER 2 RESTROSPECTIVE STUDY OF VISUAL AND REFRACTIVE DEVELOPMENT OF CHILDREN WITH DOWN'S SYNDROME AND NYSTAGMUS

2.1 Introduction

Studies conducted to establish visual acuity (VA) norms in typically developing children have been reported for decades (Teller et al. 1986; Van Hof-Van Duin and Mohn 1986; McGraw and Winn 1993; Salomao and Ventura 1995; Shea and Gaccon 2006; Saul and Taylor 2012). However, due to the different cognitive abilities of children at different ages, it is difficult to use a single VA measurement technique across all ages. Therefore, different tests have been used to measure VA in children at different ages. Some studies have focused on using the preferential looking technique to measure VA development in infancy (Courage and Adams 1990; Salomao and Ventura 1995), while others have established norms for a single specific test and a narrower age range (Adoh and Woodhouse 2003; Saul and Taylor 2012). Since a visual acuity score is highly dependent on the test used (Anstice et al. 2017; O'Boyle, Chen and Little 2017) it is difficult to establish exactly how acuity develops and when it reaches an adult level. Generally, acuity is poor in the early weeks of life and improvement is rapid over the first year (Courage and Adams 1990).

2.1.1 VA in children with DS

Children with DS have been reported to have poorer VA than the expected norm (Courage et al. 1994; Woodhouse et al. 1996; John et al. 2004; Little et al. 2007; Little et al. 2009; Tomita 2017; Zahidi et al. 2018). Visual acuity in children with DS is mostly measured with refractive correction (Woodhouse et al. 1996; John et al. 2004; Little et al. 2007; Little et al. 2009; Zahidi et al. 2018) and children with nystagmus or any other visually impairing condition are often

excluded from VA studies of children with DS (Little et al. 2007; Little et al. 2009; Tomita 2017; Zahidi et al. 2018).

One study explored whether motivation and attention were the cause of the limitation in visual performance of children with DS by comparing visual evoked potential (VEP) and behavioural VA of children with DS and typically developing children as controls (John et al. 2004). The authors discovered that children with DS had significantly poorer behavioural VA and VEP compared to the control group. They also found a positive correlation between behavioural VA and VEP in the DS group, suggesting that the poor VA in these children is not attributable to attention or motivation as VEP measurements do not require attention and motivation.

VA deficits in children with DS have been associated with degradation in the optical quality, as shown by measurements of interferometric acuity (Little et al. 2007). To investigate the effect of optical quality on the visual performance Little et al. (2007) compared three different types of acuity: detection acuity, resolution acuity and interferometric acuity of children with DS and typically developing children as controls. The authors found no significant difference between the three types of acuity in the control group. However, children with DS showed a significantly poorer recognition and resolution acuity (mean VA 0.33±0.18 logMAR and 0.48±0.09 logMAR respectively) compared to interferometric acuity (0.003±0.006 logMAR). The poor resolution acuity and relatively good interferometric acuity of children with DS found in this study suggest that the visual performance of these children is limited by the optical quality and their retina are well functioning.

The most comprehensive evaluation of the development of visual acuity in children with DS up to the age of 12 years is that by Zahidi et al. (2018). In this study, binocular VA norms were established through retrospective analysis of 159 cross-sectional data of binocular VA of

children with DS from the Down Syndrome Vision Research Unit cohort at Cardiff University. Longitudinal data of 9 children over the period of 12 years were also analysed. Children with visual impairing conditions such as cataract and nystagmus were excluded from analysis.

2.1.2 VA in typically developing children with nystagmus

Two independent studies have been conducted looking into the development of VA in typically developing children with INS without (idiopathic, IIN) and with underlying ocular conditions. The first study by Weiss and Kelly (2007) focused on early infancy and a younger group of children. The second study by Fu et al. (2011) looked at a wider range of age from early infancy to adolescence. Both studies used the preferential looking method to measure VA in the younger group of children. The latter study used letter picture optotypes for VA measurement in the older group of children. Both studies found that VA was generally poorer in typically developing children with INS compared to age matched norms. Weiss and Kelly (2007) found that children with INS, both with and without underlying conditions, under the age of 4 years old had VA development that parallels the VA development norms. The study by Fu et al. (2011) agreed that the VA development rate of children with IIN did not differ significantly from norms throughout all ages. However, they found that the VA development rate of children with albinism and optic nerve hypoplasia was significantly different (i.e. slower) to that of norms. They also found that there was little or no VA deficit in children with IIN below the age of 2 years old, which contradicts the finding by Weiss and Kelly (2007), who found that there was a significant deficit in VA of children with IIN in the first year of life. This difference in the findings may be due to the difference in corrective state of the refractive error during VA measurement (Fu et al. 2011). A more recent study by Felius and Muhanna (2013) found that typical children with nystagmus had mean VA deficit of 0.23±0.19 logMAR compared to published age-matched norms.

2.1.3 VA in children with DS and nystagmus

There is little published data on VA in children with DS and nystagmus (DSN). As discussed in Chapter 1, section 1.5.2.1, a study by Felius et al. (2014) looked at VA deficit of 16 children with DSN between the age of 10 months and 14 years old. The method used for measuring VA was preferential looking or pointing with the Teller card. Eye movement recording was also performed to quantify the nystagmus by using the nystagmus optimal fixation function (NOFF) algorithm. The authors discovered that the VA deficit of children with DSN was 0.4 logMAR worse than published typical age-matched norms.

2.1.4 Refractive error

The development of refractive error in the typical population has been studied widely (Saunders et al. 1995a). Significant refractive errors commonly occur in the first year of life. The spherical refractive errors at this at this stage of life are normally distributed with a mean and standard deviation of +2.00D and 2.75D respectively (Saunders et al. 1995a). This amount of refractive error then reduces throughout childhood, a process known as "emmetropisation" (Gwiazda et al. 1993; Zadnik et al. 1993; Ehrlich et al. 1995; Saunders et al. 1995b; Ehrlich et al. 1997) By school age, the prevalence of significant refractive errors becomes very low (Gwiazda, Thorn and Bauer 1993). The occurrence of significant astigmatism is also common in early childhood, but declines with age along with spherical refractive error (Abrahamsson, Fabian and Sjostrand 1988). The reports of astigmatism in infants vary depending on the refraction technique used. Studies that used non-cycloplegic techniques reported a prevalence of 45-53% of more than 1.00D of astigmatism (Saunders et al. 1995a). Studies using photorefraction reported a higher prevalence of 65% of astigmatism more than 0.75D. Lower prevalence of astigmatism was reported for school aged children between 5 and 6 years old (Hirsch 1963). It is unclear which type of astigmatism is most prevalent during infancy. Some studies have reported a high prevalence of against-the-rule (ATR) astigmatism was most prevalent (Dobson, Fulton and Sebris 1984; Gwiazda et al. 1984;

Abrahamsson, Fabian and Sjostrand 1988), while others reported a high prevalence of with-the-rule (WTR) astigmatism (Edwards 1991).

The prevalence of refractive errors has been reported to be much higher in both children and adults with DS compared to the typical population (Gardiner 1967; Turner et al. 1990; Woodhouse et al. 1993). Significant refractive errors in infants with DS are similar to that of typical infants. However, the emmetropisation process does not happen in children with DS (Woodhouse et al. 1997); causing the degree of refractive error to increase and remain high until adulthood (Haugen, Høvding and Lundström 2001). A cross-sectional study by Al-Bagdady, Murphy and Woodhouse (2011) reported the median spherical refractive error of children with DS in 15 age groups (1 to 15 years) to be hypermetropic in all age groups. Longitudinal data of 12 children in the same study showed no significant changes in spherical refractive error in each individual child (Al-Bagdady, Murphy and Woodhouse 2011). The distribution of astigmatism in children with DS is not significantly different from typical children during infancy and preschool age, but differs significantly during primary school age with a higher prevalence (Woodhouse et al. 1997). The most common type of astigmatism seen in children with DS was oblique astigmatism (Cregg et al. 2003; Little et al. 2009; Al-Bagdady et al. 2011; Ljubic et al. 2011)

A retrospective study of children with IIN and nystagmus associated with albinism by Healey et al. (2014) showed that children with nystagmus had a wide spectrum of refractive errors, especially those with albinism. The most prevalent type of spherical refractive error seen in children in both groups of children in the study was hypermetropia. The study also discovered that children in the IIN group failed to emmetropise. With-the-rule (WTR) astigmatism has been reported as the most common type of astigmatism seen in children with nystagmus (Jethani et al. 2006; Wang et al. 2010; Healey et al. 2014). To date, there are no published data of the refractive status of children with DSN exclusively.

2.2 AIMS

The aim of this study was to determine whether there are any differences in the distribution and development of VA and refractive error of children with Down's syndrome and nystagmus compared to that of children with DS without nystagmus, by analysing retrospectively, the clinical records of children attending the Cardiff University Special Assessment Clinic.

2.3 METHODS

2.3.1 Study population

Two hundred and fifty-eight clinical records of children in the Down's Syndrome Vision Research Unit cohort at Cardiff University from the year 1992 until 2017 were examined retrospectively. The recruitment criteria were explained in detail in Zahidi, Vinuela-Navarro and Woodhouse (2018) and are duplicated here. "During the early stages of the study, children with DS from South and West Wales were identified by the Cytogenetics Department of the University Hospital Wales before being recruited through their paediatrician. Further on, recruitment for a bifocal study (Stewart, Woodhouse and Trojanowska 2005) was conducted through educational psychologists, with no concerns of visual problems. Children who did not participate in the bifocal study (due to not having accommodative deficit or could not be matched to another child) remained in the cohort. The group of children recruited until this stage of the study was not of clinical population. As word of this work started to spread out in the early 2000's, a number of families made requests to enrol their child into the cohort, usually first attending for a clinical assessment in the School's Special Assessment Clinic. Since 2015 some children with nystagmus attending the clinic were specifically invited to join the study." No exclusion criteria were fixed; however, the child must be diagnosed with Trisomy 21.

Qualified optometrists conducted optometric assessments at the children's home, school or in the clinic at the School of Optometry & Vision Sciences. Optometric tests included VA measurement, refraction, cover test and Hirschberg's test. Children who presented with

nystagmus during two or more visits were identified and grouped into the Down's syndrome with nystagmus (DSN) group. The remaining children were grouped into the non-nystagmus group (DS). Data on visual acuity and refractive error were extracted for every visit in all children. Thirty-two children were excluded due to the following reasons: 1) there were no visits where binocular acuity data were obtained (n=8), 2) the age when entering the study was over 12 years old (n=13), 3) presented with ocular condition such as cataract (n=2), and 4) were not full corrected during visual acuity measurement (n=9).

2.3.2 Ethics

This longitudinal study obtained continual and on-going approval from NHS Ethics in Wales. Study information was given to parents and written consent was obtained from the parents of all participants involved. This study was conducted in accordance with the Declaration of Helsinki.

2.3.3 Cross-sectional Data

To prevent any bias, the database, representing 1289 visits, was inspected without names (codes were used) or acuity and refractive error data. The children were allocated to age groups. The grouping was at 1-year intervals for up to 2 years, since acuity is expected to change rapidly in infancy. Thereafter, grouping was two-yearly up to 11.9 years. In our recently published study (Zahidi, Vinuela-Navarro and Woodhouse 2018), we grouped the children into 9 age groups, at 6-month intervals for up to 2 and then two-yearly up to 11.9 years thereafter. However, the number of children with DSN was low in the 0 to 5.9 months age group (n=3) in the present study; therefore, the children in both DSN and DS group were allocated into 7 age groups to enable meaningful comparison of the findings with that of typically developing children with nystagmus (Weiss and Kelly 2007; Wang et al. 2010; Felius et al. 2011; Fu et al. 2011; Healey et al. 2014). Seven age groups were created: 1 to 11.9 months, 12 to 23.9 months, 2-3.9 years, 4-5.9 years, 6-7.9 years, 8-9.9 years, 10-11.9 years.

2.3.4 Longitudinal Data

Data of children who had data for at least 6 of the 7 age groups were included in the longitudinal analysis of binocular VA and refractive error.

2.3.5 Visual Acuity Testing

The method of visual acuity measurement varied, depending on the age of the child and their cognitive ability. In this study, visual acuity was measured using preferential looking method with Teller Acuity cards (Precision Vision) (McDonald, Dobson and Sebris 1985), Cardiff Acuity test (Adoh and Woodhouse 2003), Kay Picture LogMAR test (singles or crowded) (Kay 1983), or Keeler LogMAR Crowded test (McGraw and Winn 1993). Depending on the child's cooperation, VA was measured binocularly first, and then monocularly. VA measurement with the Teller Acuity Cards and Cardiff Acuity Test was performed at 38cm or 50cm respectively. When using the Kay Pictures and Keeler LogMAR crowded test, measurement was at 3 meters. VA was recorded using Snellen notation and converted to log minimum angle of resolution (logMAR) unit for analysis. Children who had been prescribed spectacles wore their corrections during the VA measurement.

2.3.6 Refractive error measurement

Refraction was performed using the Mohindra technique in a completely dark room using a dim retinoscope light following the procedure outlined by Elliot (2014). This technique has been shown to obtain refractive error that is not significantly different from that obtained by cycloplegic refraction in children with DS (Woodhouse et al. 1997). Refractive error was recorded in sphere, minus cylinder (cyl) form and axis (º). Significant refractive error was defined as spherical equivalent refractive error (SER) of <-0.50DS (myopia) or ≥+2.50DS (hypermetropia) (Little et al. 2009). Significant astigmatism was defined as >-0.50DC and was classified into three groups: with-the-rule (WTR) for cyl axis at 180º ± 15º, against-the-rule

(ATR) for cyl axis at 90º ± 15º, and oblique for cyl axis that is greater than ± 15º from the horizontal and vertical meridian (Little et al. 2009). Data of the RE was used for analysis for all participants except for those with anisometropia (a difference of 1.00D or more in the SER between the RE and the LE) for which the data of the least ametropic eye was used (Al-Bagdady, Murphy and Woodhouse 2011)

2.4 Analysis

Statistical analysis was performed using the IBM SPSS version 23 statistical package. Descriptive analysis was performed on both VA and refractive error data to determine the mean, standard deviation (SD), median, 95% confidence intervals, and frequency of each age group for both the DSN and DS group. The distribution of binocular VA, SER and astigmatism data for each group of children at each age group was tested using the Shapiro-Wilk test for normality. Data that were normally distributed ($p>0.05$) were analysed using parametric statistical tests. Non-parametric statistical tests were used to analyse data that were not normally distributed ($p<0.05$).

2.5 Results

2.5.1 Study population

Of the 258 children in the cohort, 58 (22.5%) presented with nystagmus, of which 30 (51.7%) were male and 28 (48.3%) were female. After exclusion based on the criteria described in Section 2.3.1, a remainder of 226 children were included in the cross-sectional study which consisted of children with DSN (n=50) and DS (n=176). The distribution of children in each age group is tabulated in Table 2.1. Longitudinal data were available for 4 and 10 children in the DSN and DS group respectively.

	1-11.9 months	18-23.9 months	2-3.9 years	4-5.9 years	6-7.9 years	8-9.9 years	10-11.9 years
DSN (n)	8	9	9	9	5	5	5
Mean Age ± SD (years)	0.59 ± 0.25	1.48 ± 0.30	2.88 ± 0.47	5.15 ± 0.56	6.92 ± 0.46	8.44 ± 0.35	11.11 ± 0.79
DS (n)	38	35	25	23	23	14	18
Mean Age ± SD (years)	0.56 ± 0.23	1.45 ± 0.28	2.78 ± 0.58	4.95 ± 1.05	6.81 ± 0.69	8.86 ± 1.21	10.53 ± 0.47

Table 2.1 Distribution and mean age ± SD of children with DS and nystagmus (DSN) and without nystagmus (DS) in each age group

2.5.2 Visual acuity

Binocular VA (BVA) ranged between 0.2 and 1.4 LogMAR for the children in the DSN group and 0.0 and 1.4 LogMAR for the children in the DS group. The median BVA of children in the DSN group was 0.1 LogMAR (one line) poorer than that of children in the DS group in the first year of life and remained poor throughout all age groups. BVA of both groups of children in improved with age, although the improvement of the children in the DSN group was significantly slower than that of children in the DS group. Analysis of covariance (ANCOVA) was used to determine the effect of nystagmus on the binocular VA score with age as the covariate. There was a significant difference between the binocular VA between children with DS with and without nystagmus ($F=28.42$, $p<0.05$) with children in the DSN group having significantly poorer VA than that of children in the DS group. The mean binocular VA of both groups of children with DS with and without nystagmus was plotted against age in Figure 2.1

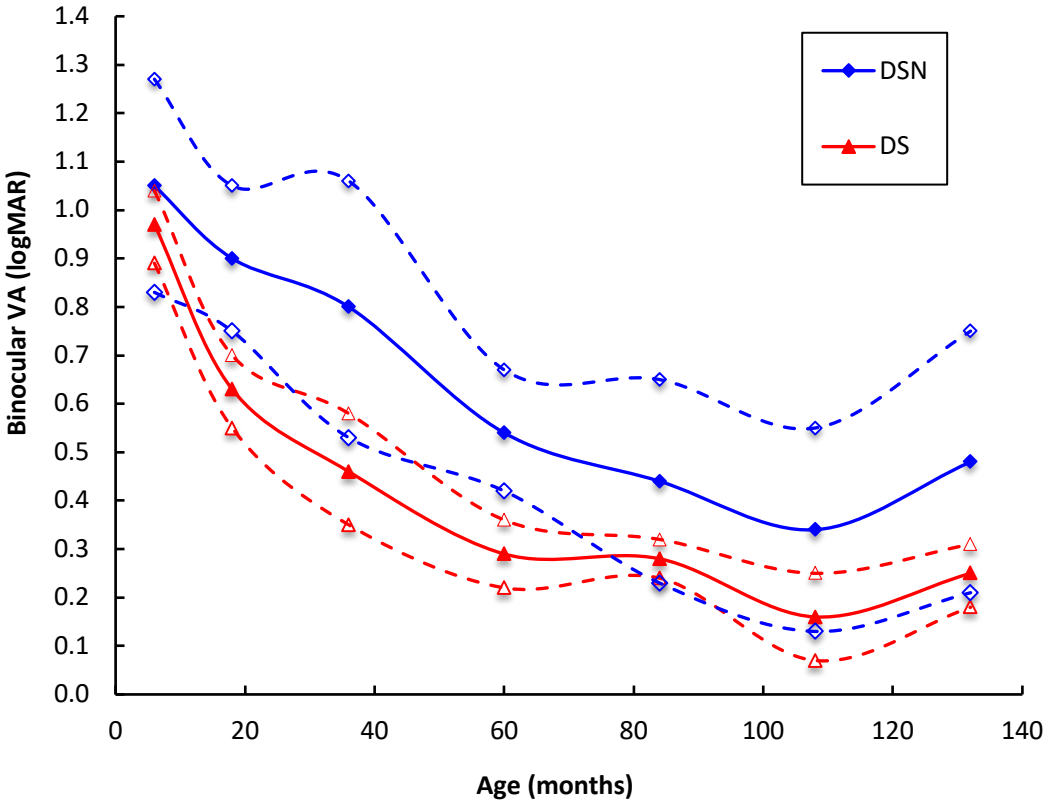


Figure 2.1 Mean binocular VA of both groups of children with DS with (DSN) and without (DS) nystagmus. Open markers with dashed lines depict 95% confidence limit

The mean binocular VA of typically developing children with idiopathic IN and IN associated with albinism reported by Fu et al. (2011) was plotted in Figure 2.2 with the mean binocular VA of children with DS with and without nystagmus from the present study to demonstrate the significant deficit in binocular VA of children with DSN compared to typically developing children. The binocular VA of children with DSN is even poorer than that of typically developing children with IN associated with albinism in early childhood. The development of binocular VA of children in the DS group is not markedly different from that of typically developing children with IIN.

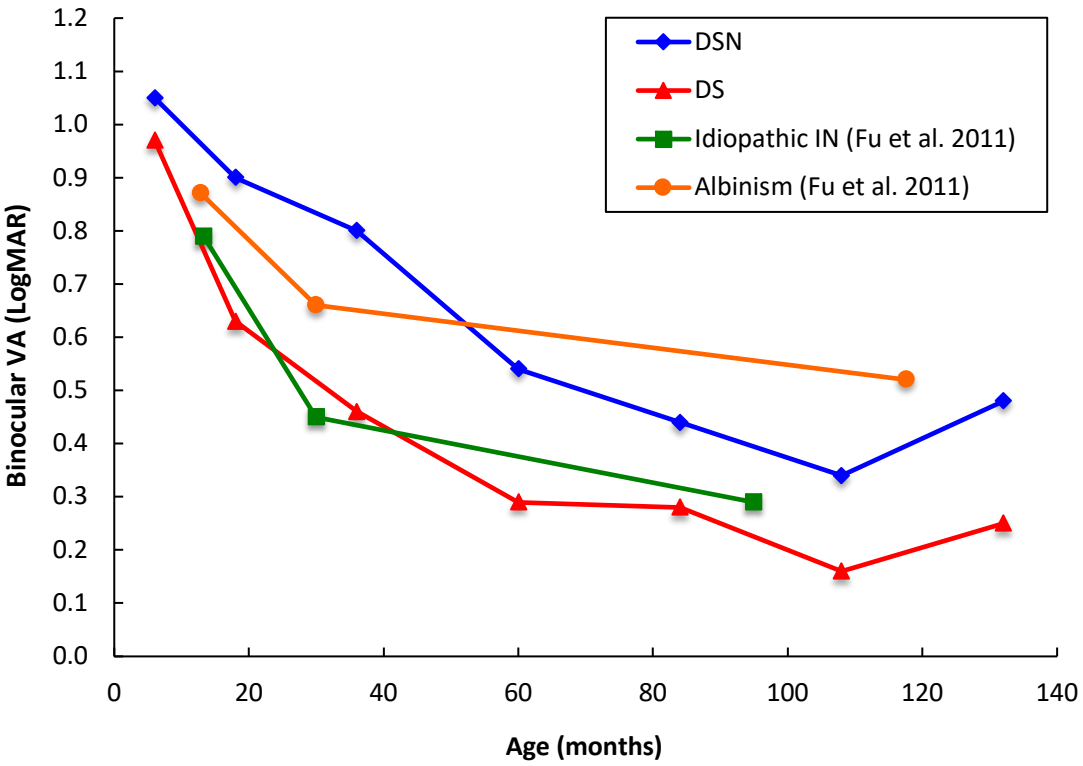


Figure 2.2 Mean binocular VA of children with DS with (DSN) and without (DS) nystagmus compared to published data of idiopathic IN ad IN associated with albinism (Fu et al. 2011)

When the distribution of binocular VA of children in the DSN group was plotted alongside published norms of each test used in the present study (Figure 2.3), only 6 (12%) of the children who were 36 months and younger had binocular VA within the 95% confidence limits of the published norms. One (2%) child fell on the 95% confidence limits, whereas the remaining children (86%) had binocular VA worse than the published age norms.

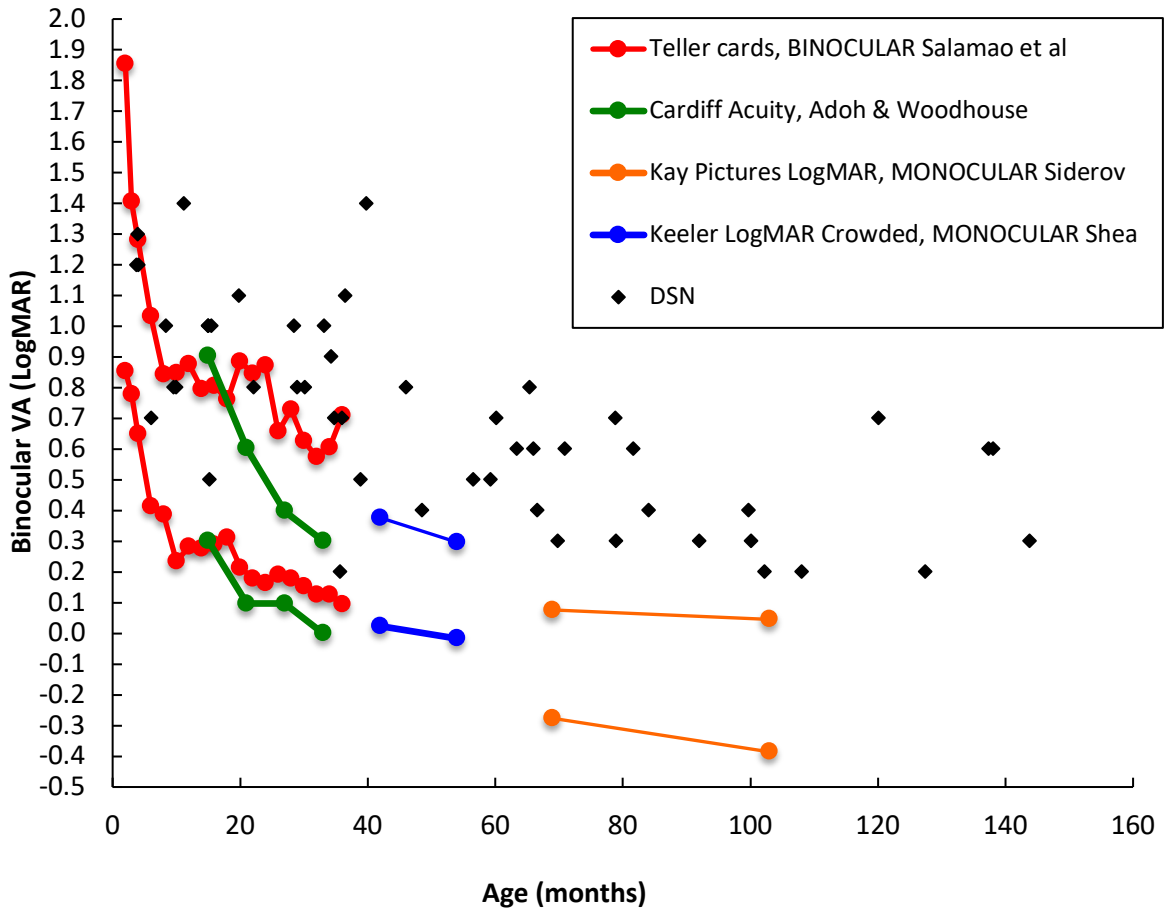


Figure 2.3 Distribution of binocular VA of children with DS and nystagmus (DSN) plotted alongside 95% confidence limits published norms of Teller Acuity Cards (Salomao and Ventura 1995), Cardiff Acuity Test (Adoh and Woodhouse 2003), Kay Picture LogMAR (Norgett and Siderov 2011), Keeler LogMAR (Shea and Gaccon 2006)

Longitudinal data for binocular VA was available for 4 children in the DSN group (Figure 2.4) and 10 children in the DS group (Figure 2.5). The progression of binocular VA for each child in both groups of children in the DS and DSN group was the same as that in the cross-sectional data and were within the 95% confidence limits of the cross-sectional data. Children in the DSN group had no binocular VA reaching 0.0 LogMAR at any age. Five children in the DS group had binocular VA reaching 0.0 LogMAR at a certain age (P035 = 10 years; P070 = 10.56 years; P074 = 8.34 years; P111 = 4.70 years; P146 = 6.8 years), but none had VA better than 0.0 LogMAR.

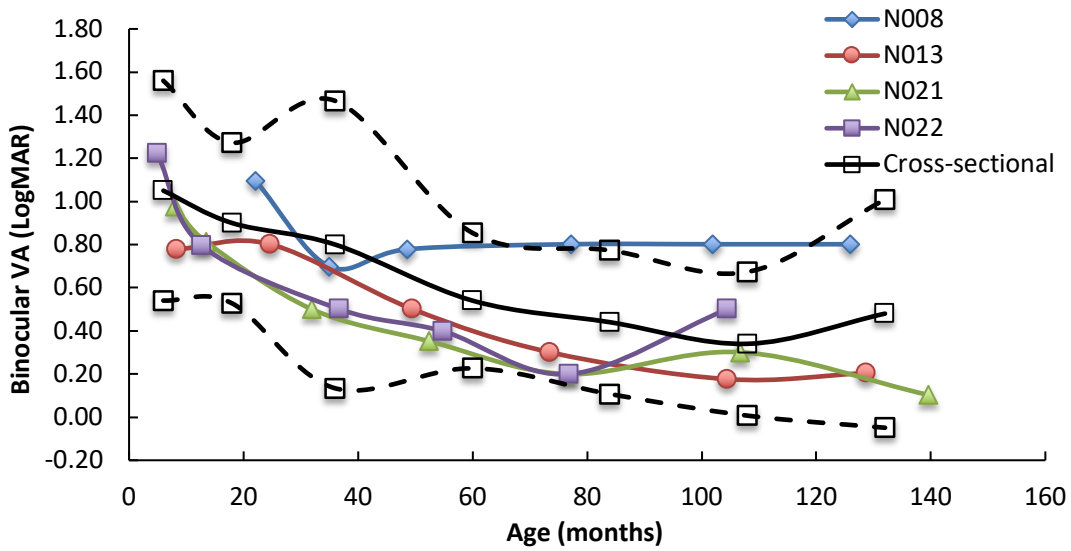


Figure 2.4 Binocular acuity of children in the DSN group followed longitudinally compared to cross-sectional data (mean and 95% confidence limit indicated by open black square markers)

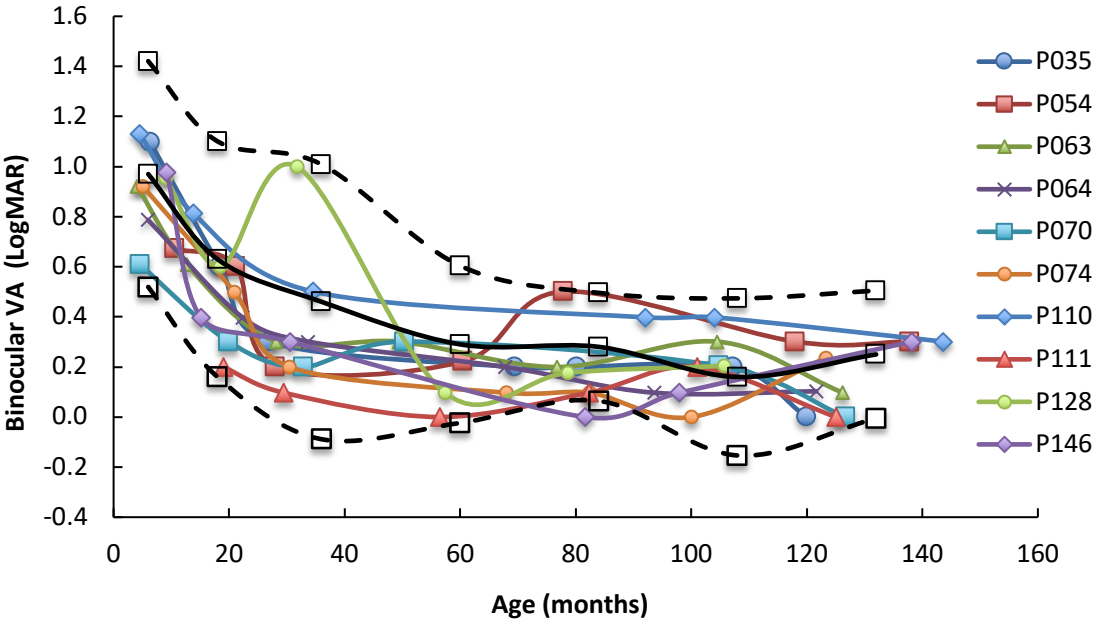


Figure 2.5 Binocular VA of children in the DS group followed longitudinally compared to cross-sectional data (mean and 95% confidence limit indicated by open black square markers)

2.5.3 Refractive error

2.5.3.1 Spherical Equivalent Refractive Error (SER)

Seven (14%) and 18 (10.2%) of children in the DSN and DS group were anisometropic respectively. Data of the LE were used for 5 children in the DSN group and 8 children in DS group; otherwise RE data were used. Spherical equivalent refractive error (SER) data of both groups of children were normally distributed ($p>0.05$) for all age groups except the 12-23.9 months ($p<0.05$) and 10-11.9 years ($p<0.05$) in the DSN group and the 12-23.9 months ($p<0.05$) in the DS group. SER of children in the DSN group was between -12.00D and +7.75D. In the DS group, the SER ranged between -10.00D and +10.38D.

Figure 2.6 show the median SER of both groups of children for each age group. Although the data were normally distributed, medians and inter-quartile ranges were used to enable comparisons of the results with that of Al-Bagdady, Murphy and Woodhouse (2011) whose data were not normally distributed. Children in the DSN group showed more variability in the SER compared to the DS group. Regression analysis was performed on SER data to determine whether SER changed with age for both groups of children. Results show that there was no significant change in SER with age for both groups of children (DSN, $p=0.936$; DS, $p=0.889$). Data for children under 1 year was removed because refractive error is likely to change (Saunders et al. 1995a). ANCOVA was then performed to determine the effect of nystagmus on SER, with age as a covariate. There was a significant difference in the SER between children in the DSN and DS group when age was taken into account ($F=8.30$, $p<0.05$) for children over the age of 1 year old.

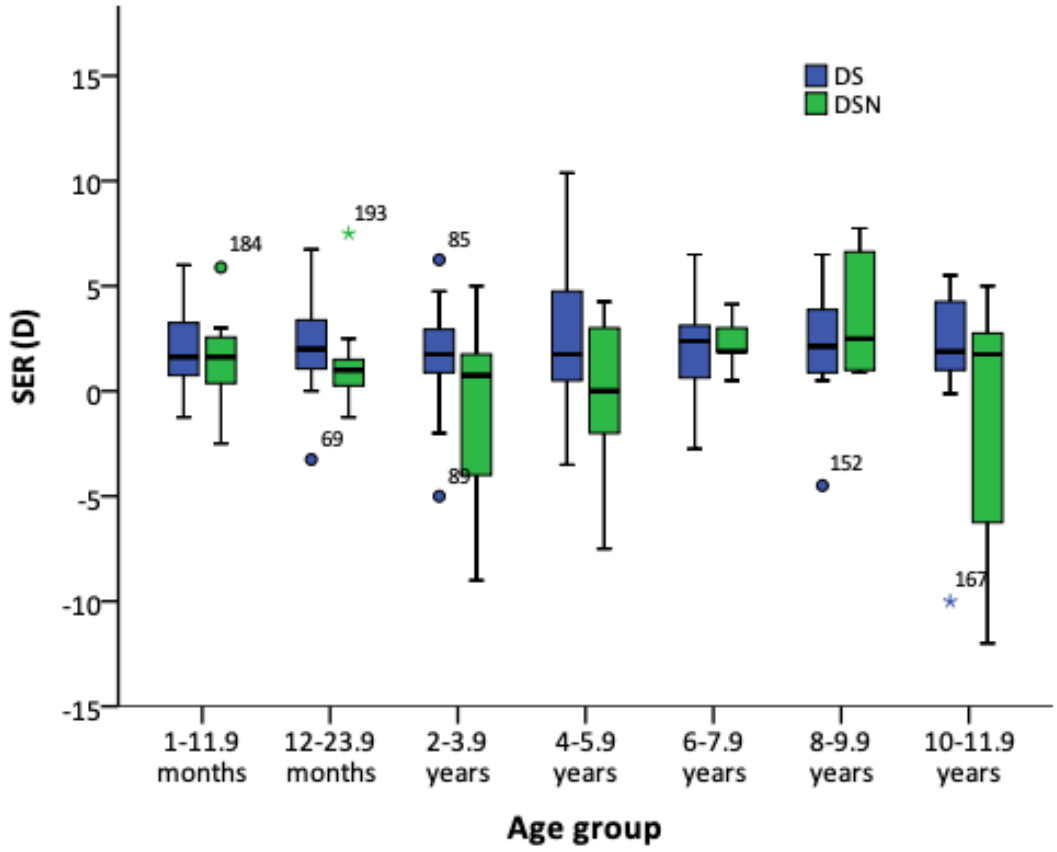


Figure 2.6 Spherical equivalent refractive error (SER) for each age group of children with DSN and DS. Box represents median and inter-quartile range (IQR). Whiskers represent minimum and maximum values excluding outliers. Circle and star represent outliers.

The SER distribution of children in the DSN group was plotted alongside SER data of typically developing children with idiopathic infantile nystagmus (IIN) reported by Healey et al. (2014). As shown in Figure 2.7, only 8 (16%) of the children in the DSN group fell outside the 95% limit of the SER of children with DS, and IIN; 7 of these were more myopic and only 1 more hypermetropic.

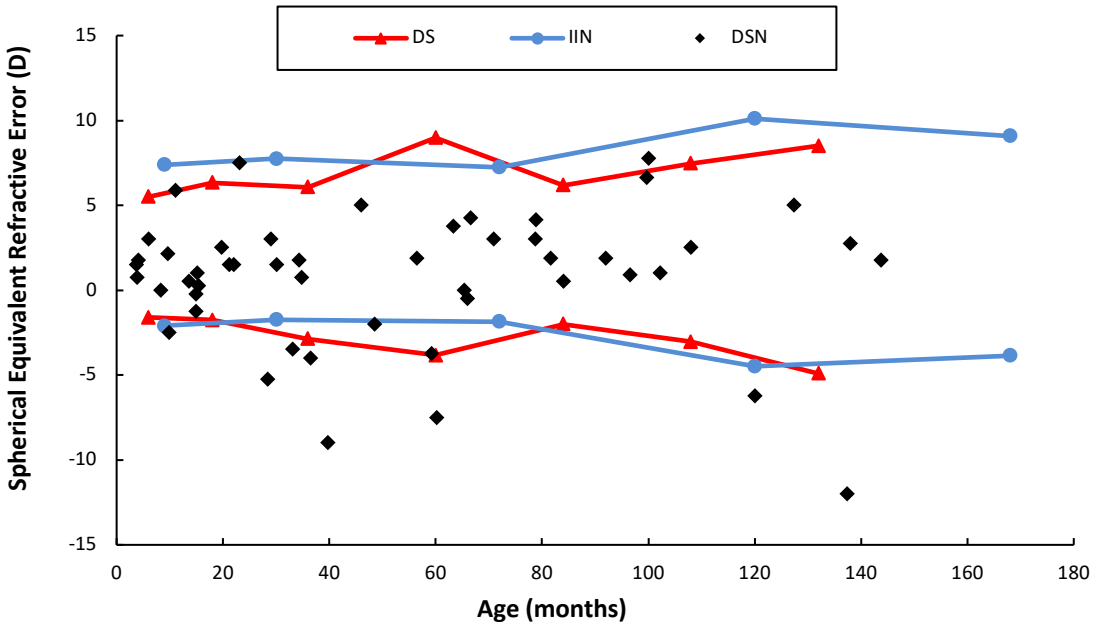


Figure 2.7 Spherical equivalent refractive error (SER) of children in the DSN group plotted alongside 95% confidence intervals of SER data of children in the DS group (red lines) from the present study and children with idiopathic infantile nystagmus (IIN, blue lines) published by Healy et al. (2014)

Figure 2.8 shows the frequency of type of refractive error for each group of children with DS. Chi square analysis was again used to determine whether the presence of nystagmus in children with DS affected the type of ametropia. There was a significant association ($\chi 2 = 13.790$, $p<0.05$) between the presence of nystagmus and the type of ametropia in children with DS. Children in the DSN group showed a significantly higher prevalence of myopia (40.7%) than the DS group (11.2%).

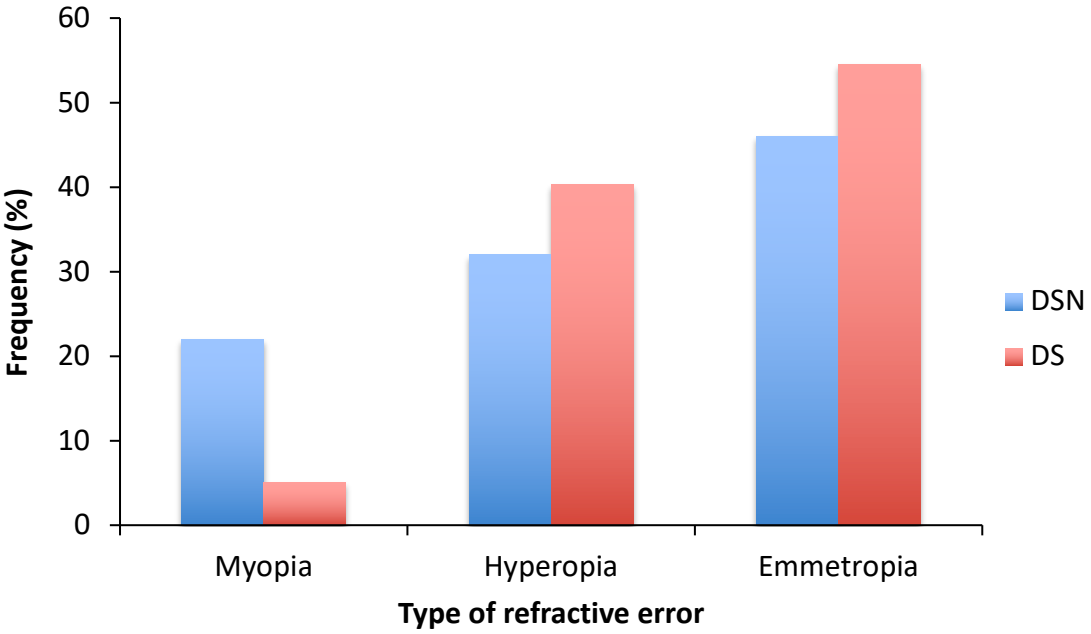


Figure 2.8 Comparison of refractive error types between children in the DSN and DS group

2.5.3.2 Significant refractive error

The prevalence of significant refractive error among children in the DSN group increased with each age group from 27.9% in the 1-11.9 months group to 80% in the 10-11.9 years group. The prevalence reduced between the ages of 6-7.9 years old but increased again between the ages 8 and 9.9 years. In contrast, the prevalence of significant refractive error in the DS group was more stable ranging between 37.5% and 57.1%. Table 2.2Table 2.3 tabulate the prevalence of significant refractive error and the different types of ametropia for each age group for both groups of children.

Age group	1-11.9 months (n=8)	18-23.9 months (n=9)	2-3.9 years (n=9)	4-5.9 years (n=9)	6-7.9 years (n=5)	8-9.9 years (n=5)	10-11.9 years (n=5)
Myopia	1 (12.5)	1 (11.1%)	4 (44.4%)	3 (33.3%)	0 (0%)	0 (0%)	2 (40.0%)
Hyperopia	2 (25.0%)	2 (22.3%)	2 (22.2%)	3 (33.3%)	2 (40.0%)	3 (60.0%)	2 (40.0%)
Emmetropia	5 (62.5%)	6 (66.7%)	3 (33.3%)	3 (33.3%)	3 (60.0%)	2 (40.0%)	1 (20.0%)

Table 2.2 Frequency of ametropia and emmetropia in children with DS and nystagmus (DSN)

Age group	1-11.9 months (n=38)	18-23.9 months (n=35)	2-3.9 years (n=25)	4-5.9 years (n=23)	6-7.9 years (n=23)	8-9.9 years (n=14)	10-11.9 years (n=18)
Myopia	1 (2.6%)	1 (2.8%)	2 (8.3%)	2 (8.7%)	1 (4.4%)	1 (7.1%)	1 (5.6%)
Hyperopia	14 (36.8%)	15 (41.7%)	7 (29.2%)	8 (34.8%)	11 (47.8%)	7 (50.0%)	9 (50.0%)
Emmetropia	23 (60.5%)	20 (55.5%)	15 (62.5%)	13 (56.5%)	11 (47.8)	6 (42.9%)	8 (44.4%)

Table 2.3 Frequency of ametropia and emmetropia in children with DS without nystagmus (DS)

2.5.3.3 Astigmatism

Mean refractive astigmatism was -0.76 ± 0.62 SD for the children in the DSN group and was -0.74 ± 0.81SD for the children in the DS group. ANCOVA was again used to determine the effect of nystagmus on the amount of refractive astigmatism in children with DS, with age as a covariate. No significant difference was found (F= 0.16, p= 0.68) between the amount of

astigmatism in children with DS with and without nystagmus for children over the age of 1 year old. Table 2.4 shows the mean and SD of refractive astigmatism for both groups of children with DS in all age groups.

Age group	1-11.9 months	18-23.9 months	2-3.9 years	4-5.9 years	6-7.9 years	8-9.9 years	10-11.9 years
DSN (mean ± SD, D)	-0.44 ± 039	-0.83 ± 0.79	-0.44 ± 0.46	-0.75 ± 0.71	-1.05 ± 0.21	-1.10 ± 0.72	-1.10 ± 0.65
DS (mean ± SD, D)	-0.67 ± 0.87	-0.54 ± 0.73	-0.63 ± 0.68	-0.72 ± 0.64	-1.21 ± 1.02	-0.91 ± 0.85	-0.78 ± 0.72

Table 2.4 Mean and SD of refractive astigmatism for both groups of children with (DSN) and without (DS) nystagmus for all age groups.

Twenty-seven (54%) of in the children in the DSN group and 102 (58%) children in the DS group had significant astigmatism. Chi square analysis showed no significant difference in the presence of significant astigmatism between children with DS with and without nystagmus ($\chi 2=1.65$, $p=0.69$). The most common type of astigmatism seen in both groups of children was WTR followed by oblique astigmatism. The frequency of the different types of astigmatism for both groups of children is illustrated in Figure 2.9. Table 2.5 and Table 2.6 summarises the prevalence of each type of astigmatism for children with DS with and without nystagmus respectively. Chi square analysis again was used to determine whether the type of astigmatism was dependent on the presence of nystagmus in children with DS. No significant difference was shown in the different types of astigmatism between children with DS with and without nystagmus ($\chi 2=1.46$, $p=0.48$).

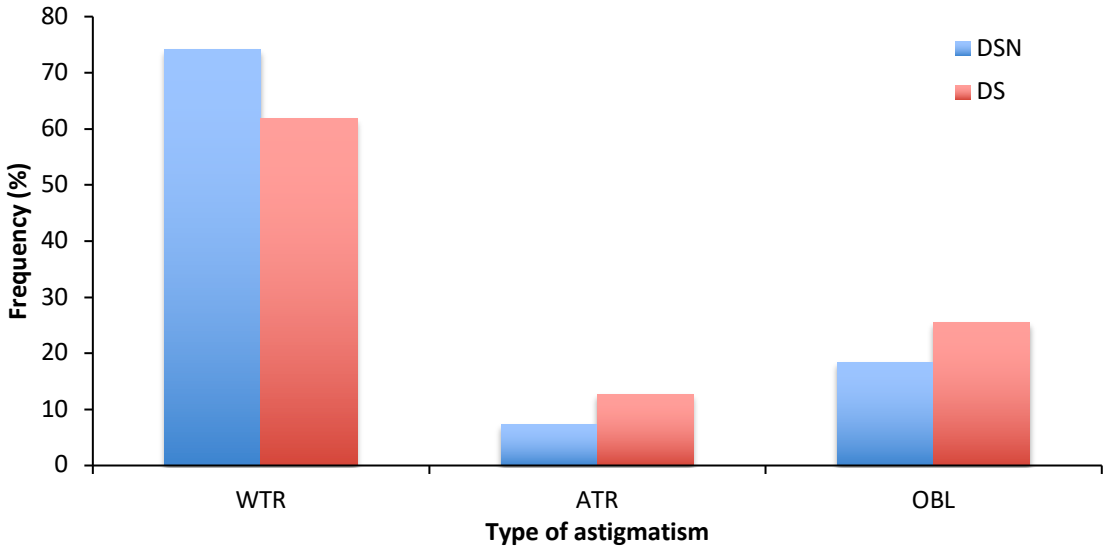


Figure 2.9 Frequency of with the rule (WTR), against the rule (ATR) and oblique (OBL) astigmatism for both groups of children with (DSN) and without (DS) nystagmus.

Age group	1-11.9 months (n=8)	18-23.9 months (n=9)	2-3.9 years (n=9)	4-5.9 years (n=9)	6-7.9 years (n=5)	8-9.9 years (n=5)	10-11.9 years (n=5)
WTR	3 (100%)	4 (80.0%)	2 (66.7%)	2 (40.0%)	5 (100%)	2 (66.7%)	2 (66.7%)
ATR	0 (0%)	1 (20.0%)	1 (33.3%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
OBL	0 (%)	0 (0%)	0 (0%)	3 (60.0%)	0 (0%)	1 (33.3%)	1 (33.3%)

Table 2.5 Prevalence of with-the-rule (WTR), against-the-rule (ATR) and oblique (OBL) astigmatism of children with DS with nystagmus in each age group

Age group	1-11.9 months (n=38)	18-23.9 months (n=35)	2-3.9 years (n=25)	4-5.9 years (n=23)	6-7.9 years (n=23)	8-9.9 years (n=14)	10-11.9 years (n=18)
WTR	17 (89.5%)	13 (72.2%)	11 (84.6%)	8 (53.3%)	4 (26.7%)	6 (50.0%)	4 (40.0%)
ATR	1 (5.3%)	3 (16.7%)	0 (0%)	3 (20.0%)	3 (20.0%)	3 (25.0%)	0 (0%)
OBL	1 (5.3%)	2 (11.1%)	2 (15.4%)	4 (26.7%)	8 (53.3%)	3 (25.0%)	6 (60.0%)

Table 2.6 Prevalence of with-the-rule (WTR), against-the-rule (ATR) and oblique (OBL) astigmatism of children with DS without nystagmus in each age group

2.6 Discussion

2.6.1 Visual Acuity

This retrospective study is the first to exclusively compare the visual and refractive status of children with DSN, which occurs in at least 15% of children with DS. The current analysis found that children with DSN have significantly poorer VA compared to that of children with DS. Visual acuity of children with DS has been shown to deviate from that of typically developing children between the age of 6 and 24 months, depending on the test used to measure acuity (Courage et al. 1994; Woodhouse et al. 1996). A recent retrospective analysis of VA data by Zahidi et al. (2018) confirms that children with DS have poorer acuity compared to typically developing children, even when the refractive errors have been corrected. The authors however, only looked at the acuity data of children with DS without any ocular conditions such as nystagmus. The study found that the VA of this group of children lies within the typical norms during infancy. However, the acuity deviates from expected norms at 3 – 4 years old. Little acuity development was seen beyond five years old. In the current analysis, I found that children with DSN have poorer binocular VA than children with DS without any ocular conditions. The difference in the median acuity of children with DSN and DS was at least 1 line. These results also reflect that of Felius, Beauchamp and Stager (2014) who also reported

visual acuity deficit in children with DSN using the Teller acuity cards. This indicates that the presence of nystagmus affects the visual performance of children with DS.

VA deficits in children with DS have been associated with degradation in the optical quality, as shown by measurements of interferometric acuity (Little et al. 2007). Children with DS have better interferometric acuity, suggesting that they have good retinal integrity, but poorer grating resolution acuity, which is affected by poor optics (Little et al. 2007). On the other hand, poor fixation stability has been associated with the VA deficit in typically developing children with INS (Felius and Muhanna 2013). Good fixation stability enables a steady image of the object of regard to be placed on the fovea, enabling good vision. The constant oscillation of the eyes in nystagmus causes unstable fixation, resulting in reduced vision. Therefore, VA deficit of children with DSN shown in this current study suggests that the combination of poor optical quality and fixation stability has a more detrimental effect on the vision of this group of children compared to typically developing children with INS and children with DS without nystagmus.

Visual acuity of children with DS was noted to deviate from published norms as early as 24 months (Woodhouse et al. 1996). The acuity of children with DSN analysed in this study was poorer than that of children with DS even in the first year of life and remained significantly poorer throughout all ages. The rate of acuity improvement in children with DS was found to deviate from published norms at approximately 3-4 years old (Zahidi et al, 2018). The rate of acuity improvement in children with DSN seen in the current analysis seemed to deviate from that of children with DS since early infancy and progress mildly throughout all ages. It can be argued that the use of different acuity test can affect the results of VA. However, Zahidi et al. (2018) showed that there was no significant difference in the acuity results between PL and optotype tests when age was taken into account. Therefore, measurement of VA using the appropriate test depending on the child's cognitive ability (Teller Acuity Test or Cardiff Acuity Test for PL; Kay pictures or Keeler letters for optotypes) in this study is justified.

VA deficit of children with INS has been associated with the onset of binocular visual deprivation and the change in the nystagmus waveform (Felius and Muhanna 2013). Typically developing children with INS usually present with triangular waveforms during infancy, which transforms into pendular and then to jerk waveforms (Reinecke, Guo and Goldstein 1988; Gottlob 1997; Hertle et al. 2002). The changes in the waveform type means changes in the foveation strategy, which underlies the visual performance in INS (Felius and Muhanna 2013). Reinecke et al. (1988) speculates that children with INS adopt new foveation strategies as they try to focus on the objects that interest them, hence, encouraging the change in the nystagmus waveform type. Therefore, the onset of change from pendular to jerk nystagmus is crucial to the visual development of children with nystagmus. Since longitudinal data were only available for 4 children with DSN, it is difficult to estimate when the nystagmus onset was for this group of children. Longitudinal eye movement recording data would be ideal to determine any changes in the nystagmus waveforms.

One of the limitations of the current study is that VA was measured with their current spectacles and not necessarily with the children's best correction, as testing acuity while wearing a trial frame can distract the children, which may affect their performance during the test. Although there could have been some changes in refractive error, this is likely to be small because the children were seen in the clinic at regular intervals. Previous published studies of VA in typical children with and without nystagmus did not measure best corrected visual acuity (BCVA) (Salomao and Ventura 1995; Adoh and Woodhouse 2003; Shea and Gaccon 2006; Norgett and Siderov 2011). Indeed, one study (Saul and Taylor 2012) did not even measure refractive error at all before testing VA. However, it is evident in Figure 2.2 that VA of children with DSN is a lot poorer than that of typically developing children with INS. The visual acuity of the typically developing children with INS in the study by Fu et al. (2011) was also measured using 'habitual optical correction'. Children with DS have been reported to have poorer VA than the expected norm (Courage and Adams 1994, Woodhouse et al. 1996, John et al. 2004, Little et al. 2007, Little et al. 2009, Tomita 2017), despite refractive errors

being corrected. None of the published norms used in this study measured acuity with the children's best correction. In light of that, more than 85% of the BVA fell below the 95% confidence limits of typically developing children with INS and children in the DS group. Weiss and Kelly (2007) showed acuity deficit in typically developing children with INS at an earlier age, when VA of children younger than 3 years old was measured without optical correction. In contrast, the study by Fu et al. (2011) found little acuity deficit in the first 2 years of life when VA was measured with optical correction.

2.6.2 Refractive error

Refractive error of children with DSN differs significantly from that of children with DS who do not have nystagmus over the age of one year old. Although both groups of children were hypermetropic since early infancy, children with DSN were found to be less hypermetropic. The difference in the median was because there were more myopic children in the DSN group compared to the DS group.

Children with DSN in the present study showed a wide range of refractive error with larger variability compared to children in the DS group. Children with DS have been reported to have a wider distribution of refractive error compared to typically developing children with no ocular condition (Woodhouse et al. 1997; Al-Bagdady, Murphy and Woodhouse 2011). During infancy, both typically developing children with no ocular condition and children with DS show similar levels of hypermetropia. As they get older, the range of refractive error of typically developing children shifts towards emmetropia, a process known as emmetropisation. In contrast, the range of refractive error of children with DS broadens with age, suggesting that this group of children do not emmetropise. Children with IIN also have been shown to have unconventional refractive development. This population of children also presents with a wide range of refractive error and no emmetropisation (Healey et al. 2014). Despite being more hypermetropic, the refractive development pattern of children in DS group in this study was

congruous to that of typically developing children with IIN reported by Healy et al. (2014). No consistent pattern however, was seen in the refractive error development of children in the DSN group. Nonetheless, a majority (84%) of the children with DSN had refractive error within the 95% limit of SER of children with DS from this study and SER data of typically developing children with IIN.

Hypermetropia was also the most prevalent type of ametropia for both groups of children discovered in this study. Although hypermetropia was the most prevalent type of ametropia, children with DSN showed a higher prevalence of myopia compared to children in the DS group. Previous studies have shown that there is an association between congenital heart defect and nystagmus in children with DS (Bromham et al. 2002; Kranjc 2012a). There was also an association between congenital heart defect and myopia in children with DS (Bromham et al. 2002). Therefore, it is not surprising that there are more myopes in the DSN group of children.

The development pattern of astigmatism in children with DS has been reported to differ significantly from typically developing children with no ocular conditions (Al-Bagdady, Murphy and Woodhouse 2011; Little, Woodhouse and Saunders 2009; Haugen, Høvding and Lundström 2001). Typically developing children commonly present with ATR astigmatism during early infancy, which then develops into WTR astigmatism during early childhood, and usually disappears by the age of 4 years old due to the emmetropisation process. In contrast, children with DS present with WTR astigmatism since early childhood, which then develops into oblique astigmatism later during their childhood. Our analysis of the type of astigmatism in children with DS without nystagmus agrees with these findings as shown in Table 8. The prevalence of WTR astigmatism was significantly higher during the first 4 years of life but became lower from then onwards. The prevalence of oblique astigmatism was very low during early infancy but increased with age and was highest between the age of 10 and 11.9 years old. The prevalence of ATR astigmatism was the lowest amongst the three types and

remained the same across all age groups. On the other hand, children with DSN demonstrated a different pattern of astigmatism development. A large majority of the children in the DSN group presented with WTR astigmatism. Only one child in the 18-23.9 months and 2-3.9 years age group presented with ATR and only 3 children in the 4-5.9 years age group presented with oblique astigmatism. This suggests that children with DS and nystagmus tend to have WTR astigmatism compared to their counterparts who do not have nystagmus. This finding is consistent with those of previous studies reporting that a majority of typically developing children with IIN presents with WTR astigmatism (Jethani et al. 2006; Wang et al. 2010).

2.7 Summary

The results of this this study have shown that children with DSN have poorer VA than children with DS, in a similar manner to typically developing children with nystagmus have poorer acuity than children without nystagmus. There was no difference in astigmatism between children with DSN and DS, which is in contrast to typically developing children who had higher prevalence of astigmatism compared to their counterpart without nystagmus. The reason for this could be explained by the fact that children with DS in general are known to have high prevalence of astigmatism. Therefore, having nystagmus does not make it any more likely for this group of children to get astigmatism. Finally, the findings of this study showed that children with DSN had similar total refractive error to children with DS, but myopia was more prevalent.

CHAPTER 3 GENERAL METHODS

3.1 Subjects and recruitment

I aimed to study the eye movement of 4 groups of children: children with DS with nystagmus, children with DS without nystagmus, typically developing children with nystagmus and typically developing children with no ocular conditions (as controls). Children with DS with and without nystagmus were recruited through our research cohort and through the Special Assessment Clinic, Cardiff University. Recruitment of children with nystagmus without DS was through the University Hospital of Wales (via Mr Patrick Watts) and Nystagmus Network. The control groups were either siblings of the children in the study groups or children of staff members/students of Cardiff University. Recruitment of children through the clinic (and their siblings) received the approval of the South-East Wales NHS Research Ethics Committee (REC) and the Research and Development Departments of the University Health Board that acted as Participant Identification Centers (PIC) (Cardiff and Vale and Abertawe Bro Morgannwg). Recruitment of children of staff or students in the control group received the approval of the School of Optometry and Vision Sciences Research and Audit Ethics Committee. Children with strabismus were included in the study as there is a high prevalence of strabismus in both groups of children Down's syndrome (Yurdakul, Ugurlu and Maden 2006; Ljubic, Trajkovski and Stankovic 2011) and infantile nystagmus (Abadi and Bjerre 2002). Excluding the children with strabismus would reduce the number of samples in this study. Study information sheet was given, and all procedures were undertaken with parental consent and in accordance with the guidelines of the Declaration of Helsinki. All ethical approvals, study information sheets and consent forms are attached in Appendices A to F.

3.1.1 Sample size

The sample size for each group of subjects in this study was calculated using the following formula to compare two independent means by Snedecor and Cochran (1989):

$$n = \frac{2K\sigma^2}{\Delta^2}$$

where K is the value at 5% α-level with power of 90%, σ is the standard deviation (SD), and Δ is the expected change.

An SD of 0.99 was used to calculate the sample size. This value was obtained from the total area of eye positions of adults with nystagmus while using a 2º animated stimulus in pilot study 1 (see section 3.2.4, Table 2). The value of K was 10.5 at 5% α-level with power of 90%. The aim was to detect a difference in the eye movement values that is 1.5*SD, which is 1.49. Therefore, the sample size required for this study was:

$$n = \frac{2(10.5)(0.99)^2}{(1.49)^2}$$

$$= 9.27 \approx 9 \text{ subjects in each group}$$

As the subjects consisted of young children with nystagmus, it was predicted that there would be variability in the eye movement data and potential drop out. To overcome this, an extra 50% was added to the number of subjects. Therefore, I aimed to see a total of 13 children in each group. However, taking into account challenges discussed in section 4.3 which might limit successful recording, the absolute minimum number that must be achieved is 9 children in each group to obtain meaningful findings. The minimum number of participants required for each group in this study was similar to the number of typical adult participants with nystagmus (n=8) in a recently published study by Dunn et al. (2017).

3.2 Optometric tests

3.2.1 General health and ocular history

The parents were asked about the history of the participant's general and ocular health at the beginning of the eye tests. This included information on the participant's birth history, whether the participant had any heart condition, and when the nystagmus (if any) was noticed. Contact details for the participant's ophthalmologist were obtained from the parents. Letters were sent to their ophthalmologists who were asked to confirm the diagnosis of the type of nystagmus, i.e. infantile/congenital nystagmus, latent nystagmus (representing FMNS) or unknown/unsure. For those who were diagnosed with INS, the ophthalmologists were asked if the nystagmus was associated with any ocular conditions or not. If there was an associated condition, they were asked to state what the condition was.

3.2.2 Visual acuity

As described in Chapter 3, the method of visual acuity measurement varied, depending on the age of the child and their cognitive ability. Acuity was measured using either a preferential looking method (Teller 1979) with Teller Acuity cards (Precision Vision), or Cardiff Acuity Test (Kay Pictures) or measured using standard optotypes with the Kay Picture test (Kay Pictures), as shown in

Figure 3.1. Depending on the child's cooperation, VA was measured binocularly first, and then monocularly. VA measurement with the Teller Acuity cards and Cardiff Acuity Test was performed at 38cm or 50cm, respectively. However, when using the Kay Picture test, measurement began at 3 meters and the distance was reduced if necessary, depending on the child's performance.

Figure 3.1 Different visual acuity tests used, depending on the child's age or the response. a) Teller Acuity Card, b) Cardiff Acuity Test, c) Kay Pictures

3.2.3 Refraction

The response of a young child when performing subjective refraction can be unreliable. Therefore, objective refraction has been suggested as an alternative procedure to be used when aiming to determine a young child's refractive error. Refraction was performed using the Mohindra technique in a completely dark room using a dim retinoscope light following the procedure outlined by Elliot (2014).

3.2.4 Ocular alignment and motility

The Hirschberg test was performed to determine the ocular alignment of the subject by shining a handheld mini cooling fan with LED lights (Figure 3.2) aligned with the bridge of the subject's nose at the distance of 40cm. The position of the corneal reflex of each eye was observed. The fan was then moved to nine positions of gaze, to evaluate the ocular deviation. In children with nystagmus, the intensity of nystagmus was also observed at each gaze

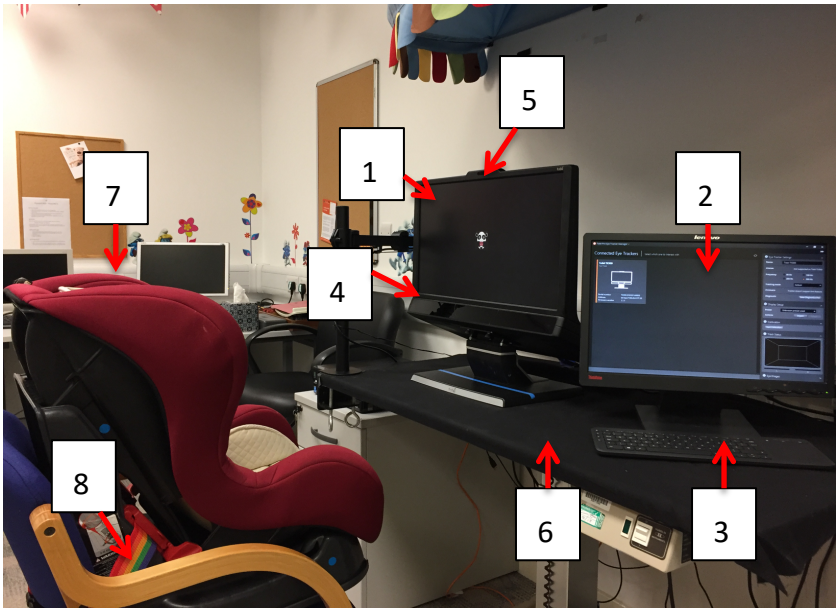
positions, to determine a null position, if any. A cover test was also performed by covering each of the subject's eyes alternately using an occluder. Besides assessing oculomotor alignment, the purpose of the cover test was also to reveal any latent nystagmus.

Figure 3.2 Mini cooling fan with LEDs (Kay Pictures) used as a target for the ocular motility test

participant's responses (e.g. head position or state of attention) during the eye movement recording, which is very useful in experiments involving children.

3.3 Laboratory set up for eye movement recording

Recording eye movements in children can be challenging due to their short attention span. The challenge of recording eye movements in children sometimes led to the eye movement data being un-calibrated (Hertle et al. 2002; Hertle and Dell'Osso 1999). Hence, a child friendly environment and the stimulus used plays a very important role when recording eye movements in young children. This study was carried out in the Children's Eye Movement Laboratory, at the School of Optometry and Vision Sciences, Cardiff University. The laboratory consisted of a spacious room allowing privacy when the eye movement recording (EMR) was performed. A car seat placed on a chair with wheels was prepared to seat children 3 years old and under. The seat was securely fixed to the back of the chair using a luggage strap to prevent the seat falling off the chair. The wheeled chair enabled the researcher to adjust the distance of the participant to be 65cm away from the eye tracker. Alternatively, if the child did not want to sit on the seat, they could sit on the parent's lap. Older children sat on the chair directly, which was height adjustable. The laboratory set up is illustrated in Figure 3.3.



Key

1. Main display screen
2. Monitoring screen
3. Wireless keyboard
4. Tobii TX300 eye tracker
5. Built in camera
6. Height adjustable desk
7. Infant car seat
8. Luggage strap

Figure 3.3 Laboratory set up for eye movement recording in children

Two eye trackers were available at the Research Unit for Nystagmus (RUN) at Cardiff University: the Eyelink 1000 and the Tobii TX300. The Tobii TX300 eye tracker was chosen for this study for a number of reasons. Firstly, it is claimed to be robust in eye tracking with some freedom of head movement. This was ideal for experiments with children, as they may not like to have their head restrained. The eye tracker uses the *pupil centre corneal reflection* (PPCR) technique, where the infrared light illuminates the eye, producing cornea reflections. The position of the corneal reflections relative to the pupil center is then calculated and is then used to determine the gaze direction (Tobii Technology 2017). The Tobii TX300 also has an infant mode incorporated into its system that changes the intensity of the illumination system for easier detection of the pupil or iris. The eye tracker comes with eye tracking software (Tobii Pro Studio) containing features that allow easy navigation of experimental procedures. In addition to that, the eye tracker has a built-in camera and microphone, which record live video and audio of the participants simultaneously with the eye movement recording. This feature of the eye tracker allows the researcher to review the

3.4 Eye movement recording

The majority of the EMR was performed in the Children's Vision Research Laboratory as described above. Additional EMRs of typically developing children with and without nystagmus (n = 7 and 1 respectively) were recorded at the Nystagmus Network open day event in September 2017. The reason for this was to ease access to the research for participants. The eye tracker was set up in a private distraction free room at the location of the event. All of the optometric tests mentioned above were performed in the same room prior to the eye movement recording except for retinoscopy. Since I was not able to acquire a dark room, retinoscopy was performed in room lighting, to obtain an estimation of the refractive error. If spectacles were available, the spectacle prescriptions were measured using focimetry.

Pre-calibration was attempted for each participant using the infant calibration program provided by the Tobii Studio^{TM} software. This involved the subject looking at a visual stimulus of a cartoon cat with sound (to maximise engagement) presented randomly at 5 different positions (upper right corner, upper left corner, lower right corner, lower left corner and centre) on the monitor screen. The stimulus first appeared at one of the five positions and jumped to the next position when the researcher judges that the child was attending to the stimulus. A calibration window was displayed after the procedure had ended, showing the quality of the calibration (Figure 3.4). In cases in which a good calibration was not achieved, the pre-calibration of the researcher's eyes was used to enable the proceeding of the EMR, as described in Chapter 4, section 4.3.2.

a)

b)

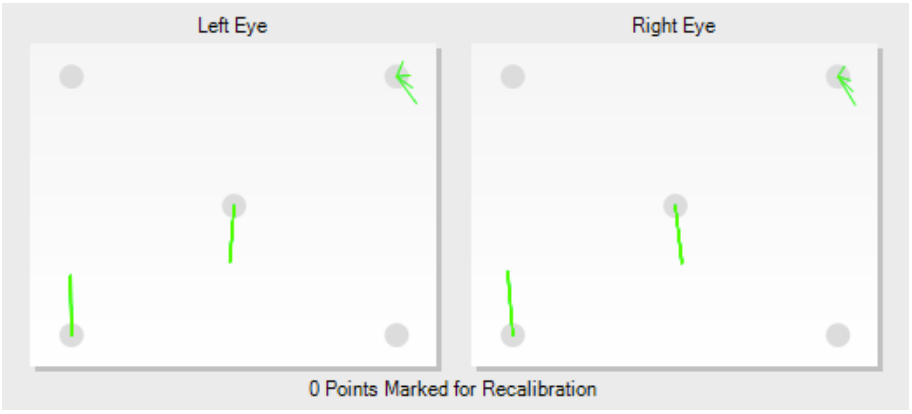


Figure 3.4 Examples of a good (a) and poor (b) pre-calibration

3.4.1 Fixation task

The task began with a start button, described in section 4.1.1, being displayed to attract the attention of the participant. The researcher then clicked the button when she was sure that the participant was looking at the screen. Each of four stimuli (see section 4.1.1) was presented for 5 seconds at the centre of the screen (0º) on a black background, eliciting 20 seconds of central fixation. An animated star was presented at the end of the task as a treat for the participants to keep them motivated. The EMR was initially recorded binocularly during this task. Depending on the cooperation of the participant, this was then followed by

monocular recording of each eye, with one eye being covered using glasses fitted with an opaque infrared pass filter (Optolite IR) made of broadband acrylic.

3.4.2 Smooth Pursuit

The smooth pursuit task used in this experiment was adapted from the study performed by Vinuela-Navarro (2015). The task, designed with a stimulus size subtending 2º and 4º of visual angle from 65cm, was accompanied by a background sound, to further attract and maintain the participants' attention (Figure 3.5). The ramp paradigm, an unexpected move of the target at a constant velocity was used. A start button was presented at the beginning of the task. When the researcher clicked the start button, the stimulus appeared 10º to the left of the screen centre, for 1 second. It then moved at a constant speed of 6º/sec to the right, stopping when it reached the position of 10º on the right of the screen centre, producing one smooth pursuit ramp. A two second fixation period was presented at this position before beginning the second ramp, in which the target moved to the left of the screen at the same speed, until reaching the 10º position to the left of centre, producing a second smooth pursuit ramp. The process was then repeated until 4 smooth pursuit ramps were produced. The total duration of the task was 23.33 seconds (see Figure 3.6).

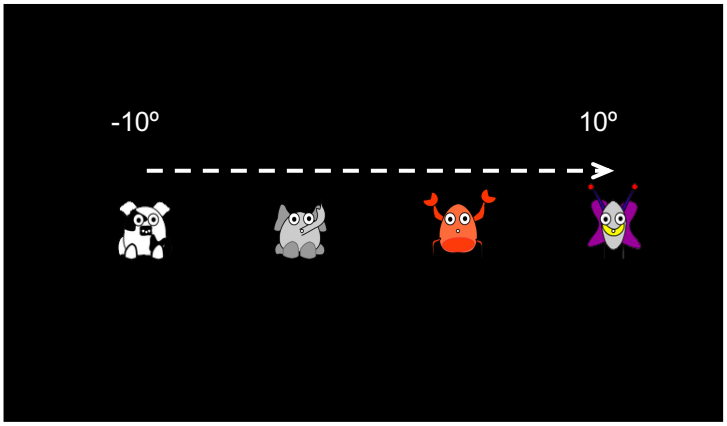


Figure 3.5 Illustration of smooth pursuit task using the cartoon stimulus created by Vinuela-Navarro (2016). The animal morphs as the target position changes

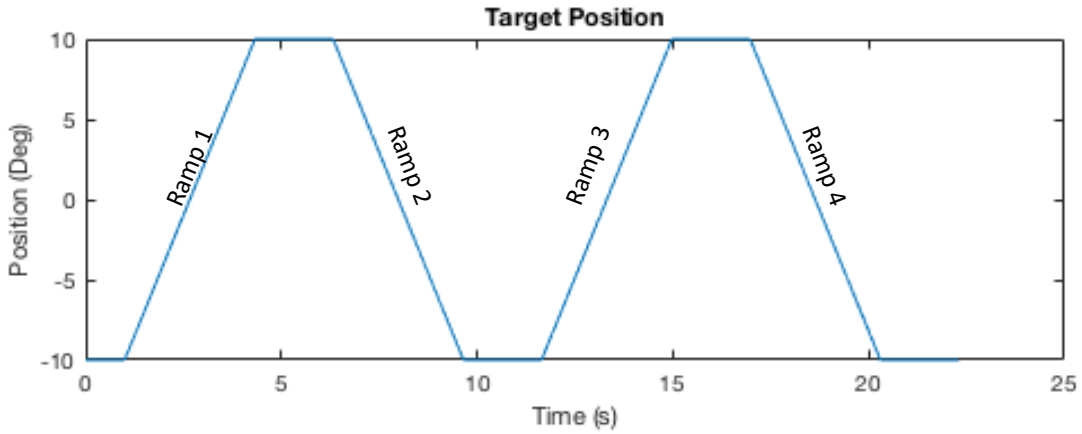


Figure 3.6 The trajectory of the target was trapezoidal, with 4 sweeps (ramps) of 3.33s of motion at 6º/s across 20º punctuated with 2s of fixation

3.5 Eye movement data output and processing

3.5.1 Selection of eye to be analysed

Raw data were exported from the Tobii Studio™ which included the task name (Studio Test Name), participant code (participant name), recording name, mouse click event, key press event, horizontal position of LE on screen (Gaze Point Left X), vertical position of LE on screen (Gaze Point Left Y), horizontal position of RE on screen (Gaze Point Right X), vertical position of RE on screen (Gaze Point Right Y), and the distance of the right and left eye from the screen (distance right and distance left respectively) in .xlsx format. The data were then imported and analysed using MATLAB. The quality of the data was inspected by plotting the horizontal eye positions of each eye against time. The percentage of available samples for each eye, mean distance of each eye from the eye tracker, and the mean pupil size of each eye were calculated. The data of the eye with the higher percentage of samples and data with the better quality were then chosen to be analysed. As early onset nystagmus is a conjugate involuntary eye movement, and our pilot study showed no significant difference between RE and LE position (see Chapter 5, section 5.2.4) data from either eye can be used.

The selection criterion for the fixation task was that the data must contain at least four nystagmus cycles with no dropped data within each cycle. This criterion was chosen to enable satisfactory analysis of the nystagmus waveform, which will be discussed in Chapter 6. The selection criteria for the smooth pursuit task was that the data must contain at least two smooth pursuit ramps, where each ramp must contain at least 50% of the calculated samples for that ramp with full nystagmus cycles.

3.5.2 Data filtering and artefact removal

Once the eye to be analysed was chosen, the raw eye position data were smoothed using a 4^{th} order Butterworth low pass filter (Behrens, MacKeben and Schröder-Preikschat 2010). The cut off frequency used was 60Hz. Artefacts (Figure 3.7a) can occur in the eye movement data due to blinks or reflections from other sources being mistaken for corneal or pupil reflection and must be removed. Artefacts in this study were detected using a jerk (change of acceleration over time) threshold algorithm, generously provided by Dr Lee McIlreavy. The algorithm detected artefacts as outliers found in the jerk distribution of the data (Figure 3.7b). Artefacts were first screened in the horizontal eye positions. A threshold value, determined by visual inspection of the jerk distribution, was used to screen for artefacts in the horizontal and vertical eye positions (Figure 3.8). Once the artefacts were found, a position trace of the horizontal and vertical eye positions with the artefacts labelled was produced for inspection (Figure 3.9). Once the researcher was satisfied with the detected artefacts, the eye position data in which the artefacts were detected were removed from both the horizontal and vertical eye positions.

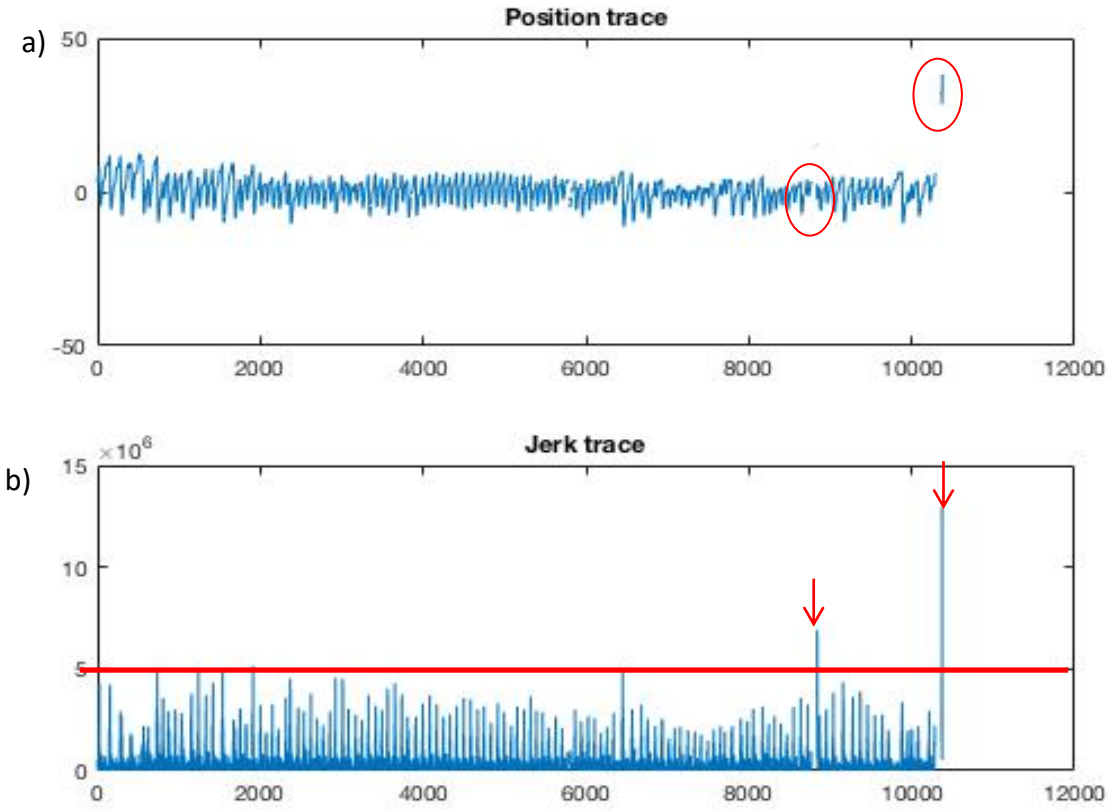


Figure 3.7 a) Position trace of participant P54 with artefacts circled in red; b) Jerk distribution showing jerks where the artifacts are (red arrow) which are beyond the jerk threshold determined (red line)

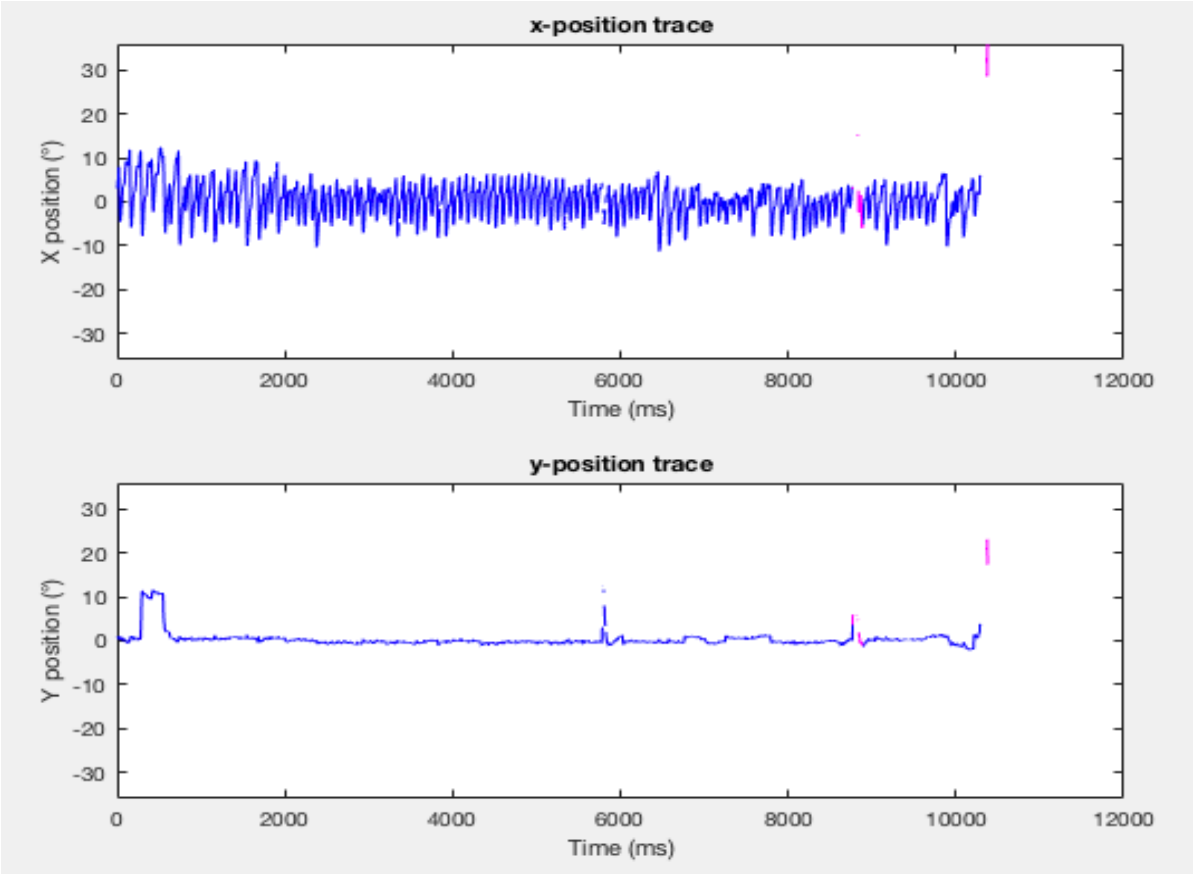


Figure 3.8 Horizontal and vertical eye traces labeled with artifacts highlighted in magenta

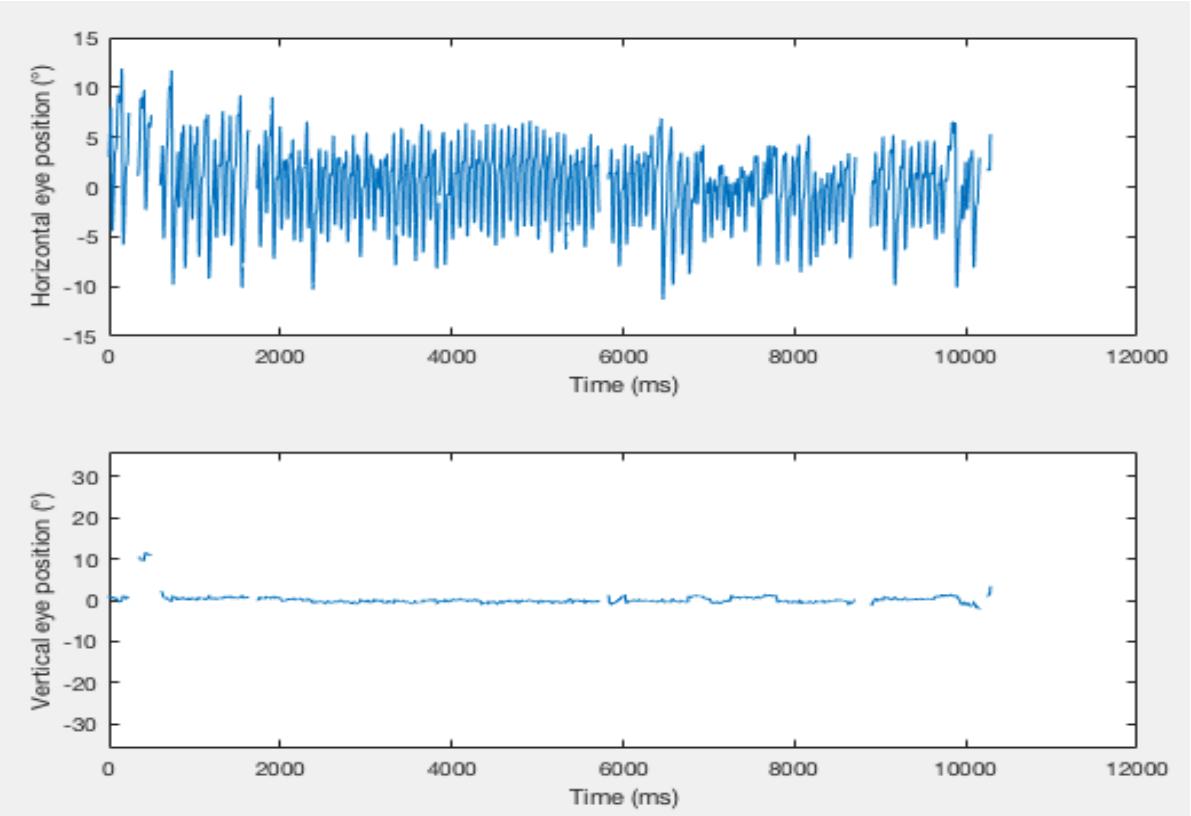


Figure 3.9 Final eye trace of participant P54 with artifacts removed from horizontal and vertical eye positions

3.6 Retrospective calibration

All eye movement data were calibrated retrospectively using the SP data as described in Chapter 5. As demonstrated in Chapter 5, there was no significant difference between the data calibrated with each of the SP ramps. Once the suitable ramp was chosen, the slope and intercept value were obtained by fitting a line to the EP vs TP plot (see section 5.5). The slope and intercept values were then used to calibrate horizontal and vertical eye positions of both SP and fixation task data (also described in section 5.5).

3.7 Saccade detection

Saccades are very fast movements of the eye from one point of fixation to another. The algorithm used to detect saccades in this study used an absolute velocity threshold. Absolute velocity of the calibrated eye position data was calculated, then the maximum and minimum points within the absolute velocity data were detected using 'peakdet', an open source function in MATLAB. The mean and standard deviation of the absolute velocity data were then calculated. The threshold value was set as the total of the mean plus one standard deviation. All maximum points exceeding this threshold value were regarded as the mid-point of the saccades. The minimum points preceding and following these maximum points were considered as the saccade onset and offset, respectively. An example of this saccade detection process is illustrated in Figure 3.10 and Figure 3.11.

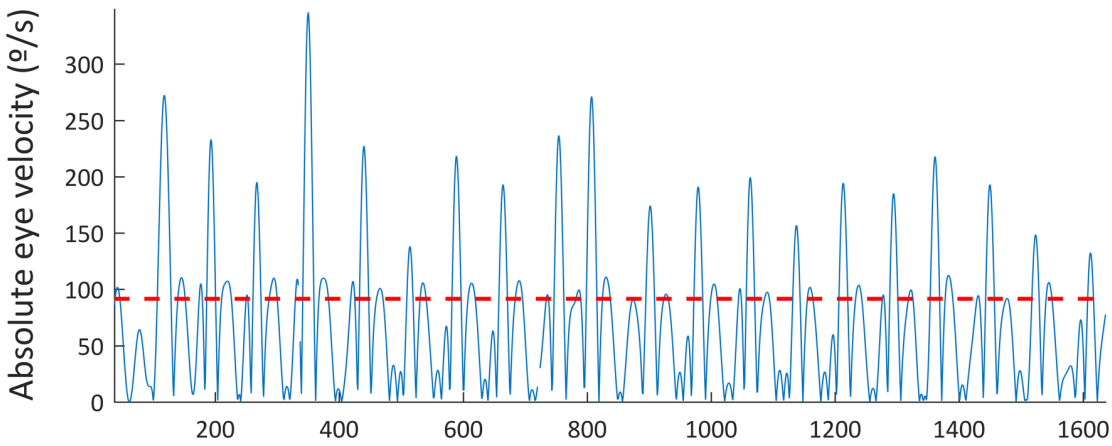


Figure 3.10 Absolute velocities of horizontal eye velocity data of participant P53. Threshold value (dashed red line) was set to the mean plus one standard deviation of the absolute velocity. Maximum points that exceed this threshold value were treated as saccades

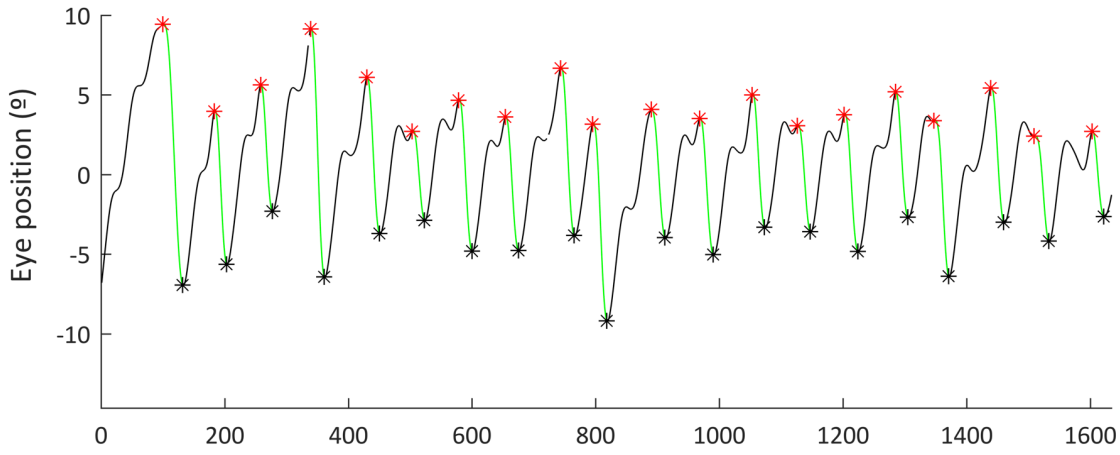


Figure 3.11 Eye trace of horizontal eye positions superimposed with detected saccades (marked in green) showing saccade onsets (red asterisks) and saccade offsets (black asterisks)

3.8 Analysis of eye movement performance in terms of accuracy and precision

Two alternative measures of eye movement (accuracy and precision) were used to compare fixation and pursuit performance of children with and without nystagmus and with and without DS in the following chapters. The measures of accuracy and precision were implemented by calculating a two-dimensional distribution of eye velocities relative to target velocities (hereby known as target-relative eye velocities). To obtain the relative eye velocities, target velocity was subtracted from the velocities of each data point in each in both horizontal and vertical eye positions for both fixation and smooth pursuit task. The product of the vertical velocity was plotted against the product of horizontal velocity (Figure 3.12). As illustrated in this figure, the data points were clustered on top of each other, making it impossible to determine the number at a given location on the diagram. To resolve this issue, a bivariate probability density function (PDF) was used. The probability of the horizontal and vertical target-relative velocities was determined and can be visualized as a two-dimensional surface in a series of isocontours (Figure 3.13). Previous studies have used bivariate PDFs to investigate the variability of eye position in typical adults (Cherici et al. 2012). McIlreavy (2016) also applied PDFs to analyze eye movement performance in adults with INS.

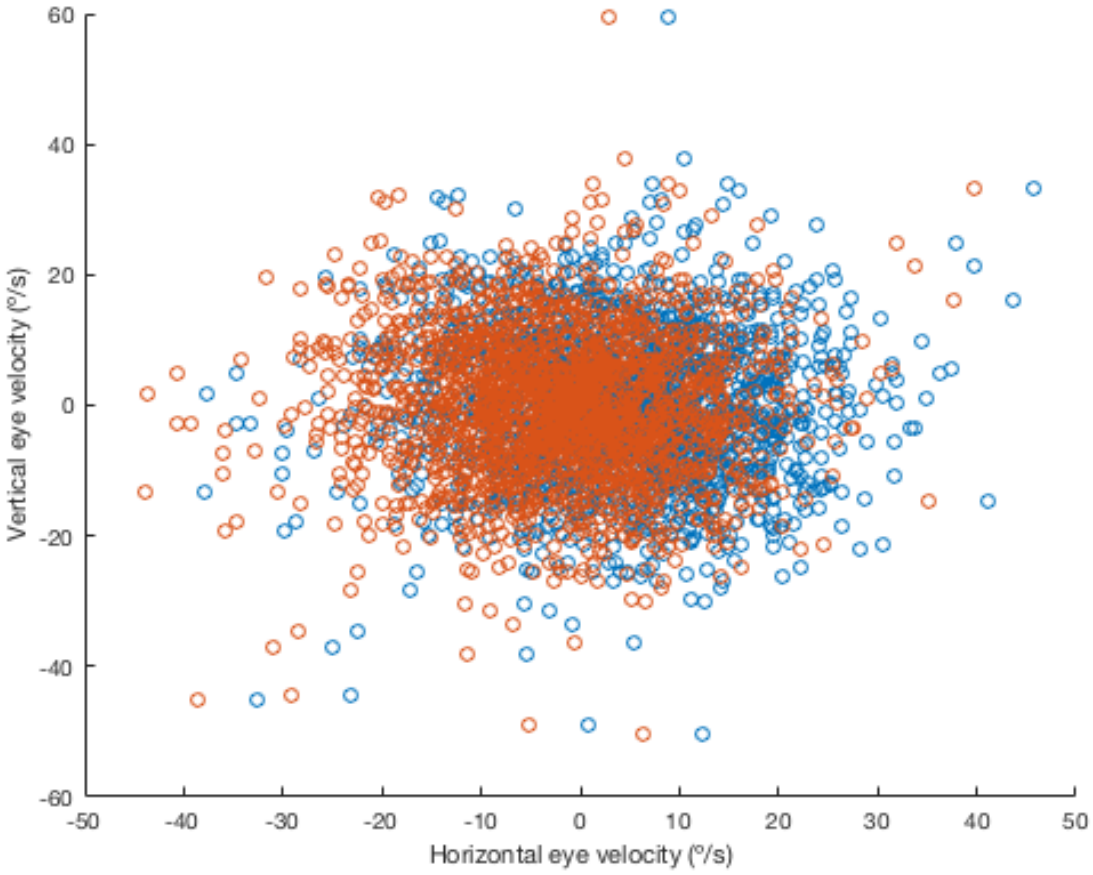


Figure 3.12 Distribution of eye velocities while pursuing a target moving at 6º/s. Blue markers represents raw eye velocities. Red markers represent target-relative eye velocities obtained by subtracting the raw eye velocities from the target velocity

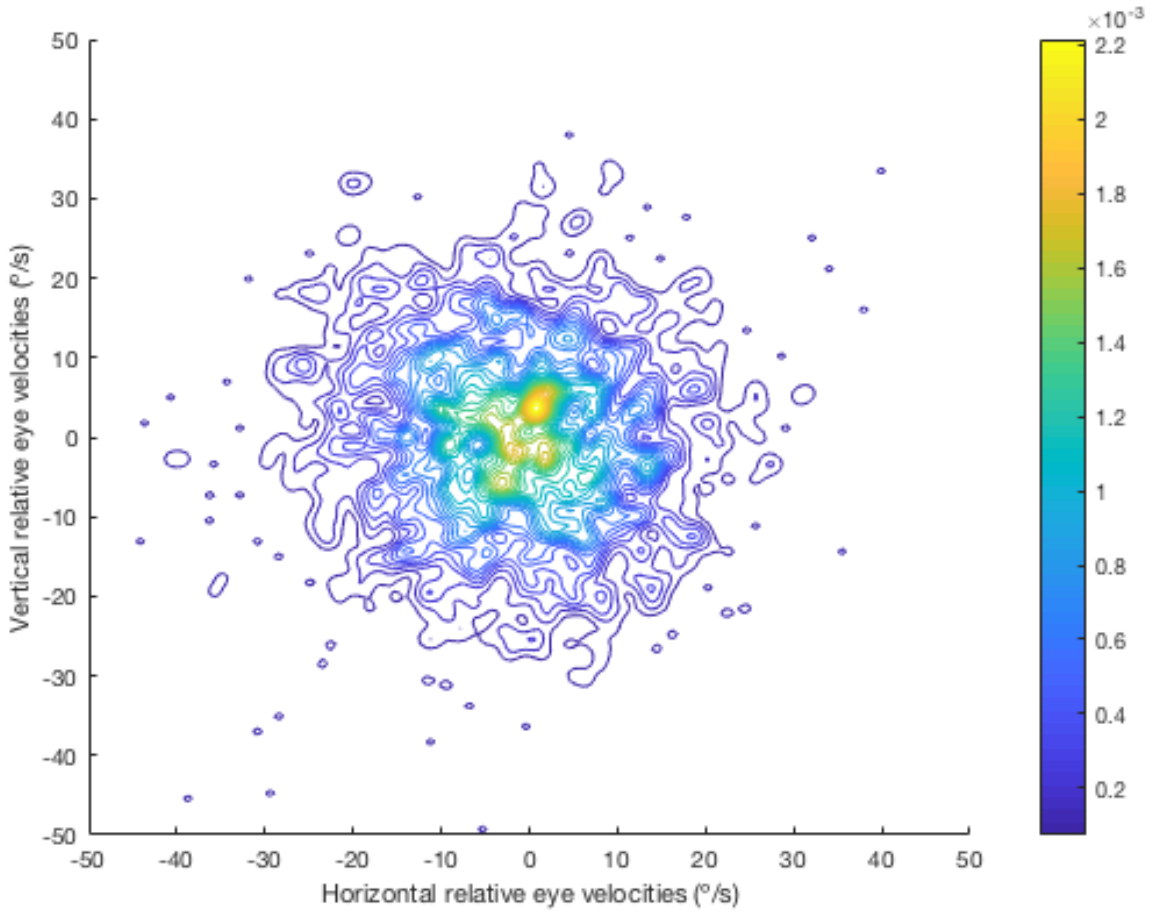


Figure 3.13 Series of probability isocontours in a 2D surface. Warmer colours depict higher probability density and cooler colours depict lower probability density

Conventionally, the variability of eye position is quantified by identifying the area in which at least 68% of eye positions occur (Crossland and Rubin 2002; Bellmann et al. 2004; Crossland, Culham and Rubin 2004; Cherici et al. 2012). Therefore, the boundaries of the area covering 68% of the most probable data were calculated. This produced an isocontour that was used to calculate the accuracy and precision of the eye movement as illustrated in Figure 3.14. The eye movement accuracy is depicted by the magnitude (termed as *accuracy rho*) and angle (termed as *accuracy theta*) to which the central point of the 68% isocontour extends. Accuracy rho informs how close the eye velocities are to the target in reference, which is the target velocity (marked by the red asterisk in Figure 3.14). The larger the magnitude, the less

accurate the eye movement is. The angle, on the other hand, represents the direction of inaccuracy; whether the eye was leading or lagging the target (McIlreavy 2016). The total area within the isocontour represents precision. A large area is indicative of a low precision. Precision can also be explained by the shape of the isocontour (hereby termed as *shape factor*). The shape factor is depicted by the ratio between the minor (short) and major (long) axis of the isocontour. A ratio of 1 suggest that the eye velocities are distributed evenly on both axes. In contrast, a ratio of 0 suggest that a majority of the eye velocities are distributed along the major axis. Figure 3.15 shows a schematic diagram of the mention eye movement performance metrics.

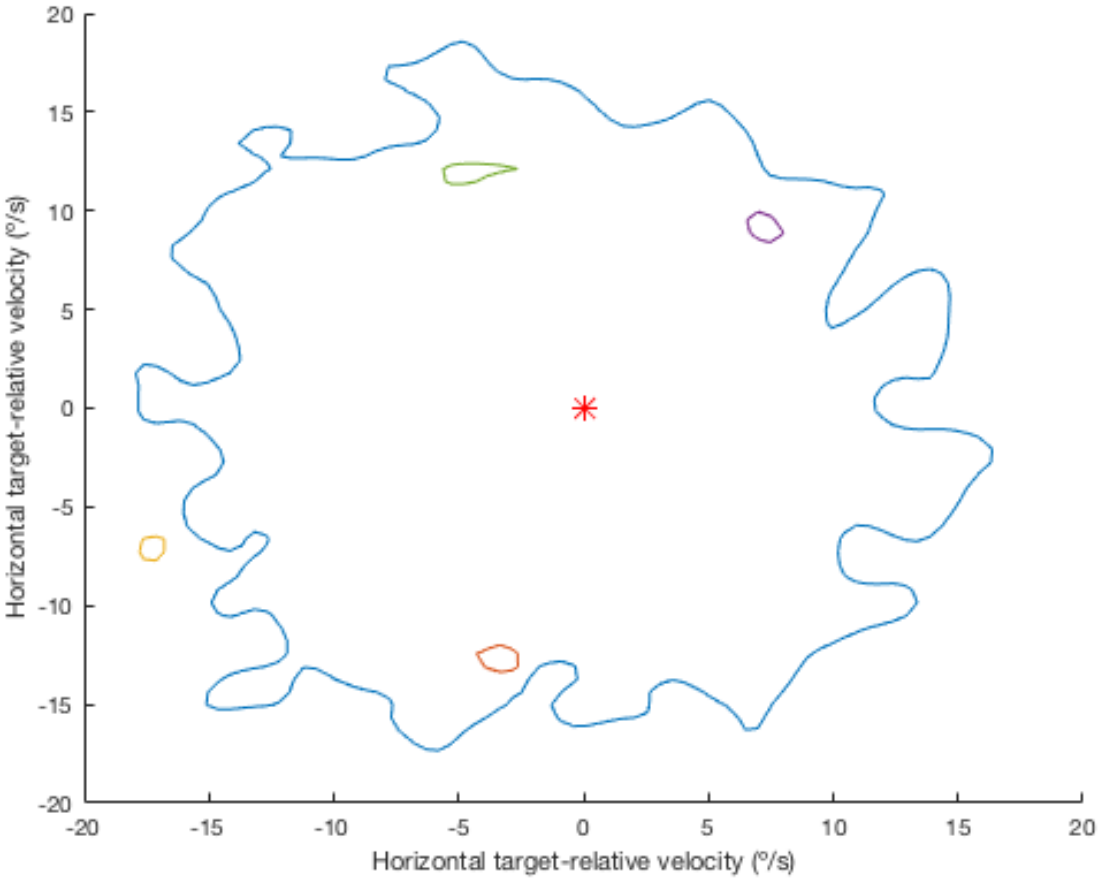


Figure 3.14 Illustration of the 68% isocontour of the PDF in Figure 3.13. The red asterisk represents the target velocity (i.e. the origin)

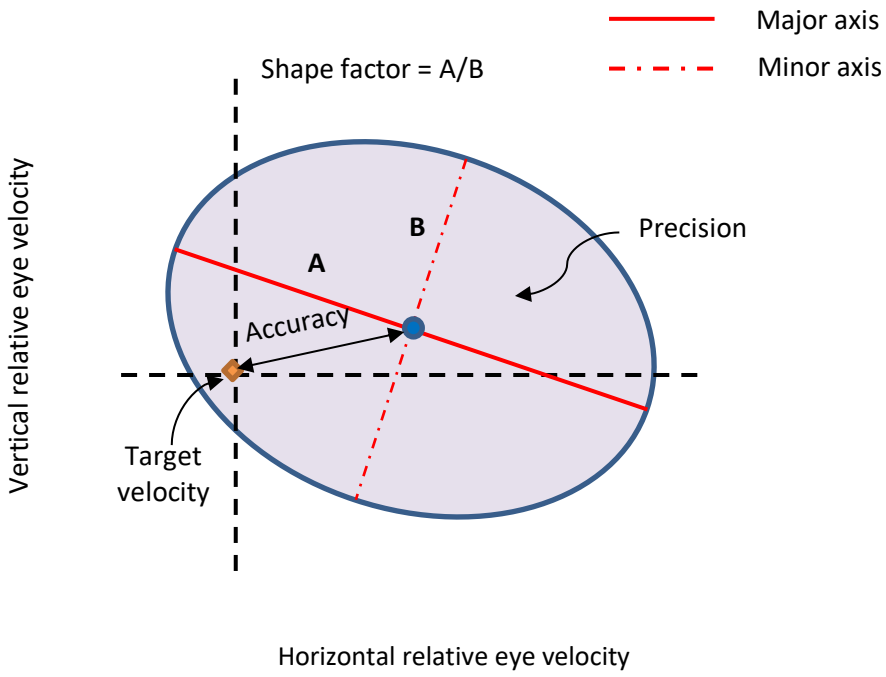


Figure 3.15 A schematic diagram of eye movement performance measures. Blue dot represents center of 68% isocontour. Accuracy is the proximity of the blue dot to the target velocity (orange diamond). Precision is the variability of the relative eye velocities (shaded area)

This technique of analysing eye movement performance was developed by McIlreavy (2016) but has only been used on typical adults with IN. In contrast, I will be using this technique to assess the eye movement performance of children with and without nystagmus with and without DS in this study described in Chapter 7.

CHAPTER 4 DEVELOPMENT OF EYE MOVEMENT RECORDING METHODS AND DATA ANALYSIS FOR YOUNG CHILDREN WITH AND WITHOUT NYSTAGMUS

4.1.1 Stimulus development

Previous studies have shown that infants younger than 5 to 6 months are more likely to recognize and pay attention to simple stimuli compared to complex ones (Rose, Feldman and Jankowski 2004). Infants between 0 to 3 months are reported to be drawn to stimuli with high contrast, well defined borders and motion, whereas older infants (3 to 6 months) tend to focus more on relevant features of objects and faces (Reynolds 2015). Therefore, a number of new stimuli that included these features were designed by me and tested to attract the attention of the children that participated in this study. Two sets of stimuli were used: one for the fixation task and another for the smooth pursuit task. The purpose of using two different sets of stimuli was to keep the children interested in the eye movement recording. Both sets of stimuli had the same characteristics, which were features of animal characters (symmetrical round or oval face shape, eye, nose and mouth), as faces are likely to attract the attention of infants more, rather than the whole body. The stimulus, of two sizes subtending 2º and 4º of visual angle from 65cm, was accompanied by a background sound, to further attract and maintain the participants' attention. High contrast colours were used in the design to better attract the attention of the infants as previous studies have shown that younger infants prefer stimuli with high contrast and defined borders (Rose, Feldman and Jankowski 2004; Reynolds 2015).

The stimuli for the fixation task were created using the software Inkscape (Free Software Foundation, Inc. Boston, USA). The design of the stimuli was adapted from an infant

application (Infant Zoo LITE: Visual Stimulation, Treebetty design, Enchinitas, CA). The images were saved in a .png format, which enabled the researcher to change the size of the stimuli when required without changing its clarity. Illustration of the stimuli used is shown in Figure 4.1. Sounds for each animal were also incorporated in the stimulus. The sounds were downloaded from www.soundbible.com and www.fresound.org, and edited using Audacity®, a free audio editor software. A start button (Figure 4.2) subtending a 4º visual angle at 65cm from the screen was presented designed and presented at the beginning of the fixation task and the smooth pursuit task described in Chapter 3. A “honking” sound was produced when the mouse cursor was hovered over the start button to attract the participant’s attention.

Figure 4.1 Illustration of the animated stimulus used in the fixation task

Figure 4.2 Illustration of the start button which produces a "honking" sound that is displayed before the start of every task

4.2 Pilot study: Effect of stimulus type and size on eye gaze stability in adult individuals with and without nystagmus

4.2.1 Introduction

Stimulus type and size play an important role in evaluating eye movement performance. Previous studies have shown that stimulus size affects the presence of pursuit eye movements (Pola and Wyatt 1985). Typically, large stimuli (≥10º) are used for young children and smaller stimuli (<2º) are used for older children (Irving et al. 2011; Grönqvist, Brodd and Rosander 2011; Pieh, Proudlock and Gottlob 2012). The effect of animating the stimuli on the EMR data quality is not certain. Recent studies on eye movement in children used cartoon images that were stationary and small (Irving et al. 2011). Although the authors did not discuss the quality of the eye movement data, it is expected that a small-sized stimulus would produce little eye movement within the stimulus area. A more recent study by Alahyane et al. (2016) used a set of 1ºx1º animated animals that grew and shrank or spun when the child fixated on the stimuli. Again, there was no description of how large the stimuli grew or the quality of the resulting eye movement data. It is predicted that larger stimuli with more detail would induce more eye movements within the stimulus area. The presence of these extra eye movements within the stimulus area would make the analysis of nystagmus waveforms more difficult, as the eyes are already constantly moving in those with IN. The bigger and more detailed the target is, the greater the variability in the positions where the fast phases redirect the eyes to, hence poorer fixation stability. The aim of the following experiment was to determine any difference in fixation the stability when using animated stimuli vs non-animated stimuli, and large stimuli vs small stimuli, of adults with IN and normally sighted adults.

4.2.2 Methods

4.2.2.1 Participants

Adults with IN were recruited from the Research Unit for Nystagmus (RUN) cohort. Normally sighted adults were recruited from the postgraduate students in the School of Optometry and Vision Sciences. Invitations for participation were sent via email.

4.2.2.2 Preliminary tests

Distance visual acuity was measured monocularly and binocularly on all participants using a 3-meter logMAR chart (Precision Vision; Illinois, USA). The spectacle corrections of the participants (if worn) were measured using a focimeter (LM-6, Topcon; Tokyo, Japan).

4.2.2.3 Eye movement recording

Eye movement recording in this experiment was performed binocularly using the Tobii TX300 eye tracker. The participants were seated 65cm away from the eye tracker, facing the screen of the eye tracker. The participants' seating position was adjusted so that their eyes were at the centre of the screen. Participants who wore spectacle corrections were asked to wear their spectacles. A calibration procedure was performed prior to the eye movement recording, using the regular calibration program provided by the Tobii Studio™ software. During the calibration procedure, a red circle was presented randomly at 5 different positions on the screen of the monitor. The participant was asked to fixate on the red circle and follow it as it moved smoothly to the different positions. A calibration window was displayed after the procedure ended, showing the quality of the calibration. The procedure was repeated if the outcome of the calibration was not satisfactory, as described in Chapter 3, section 3.3.

The participants performed 4 separate fixation tasks. The differences between the four tasks were the stimulus size and type. The stimuli in tasks 1 and 2 were 2º in size and were non-animated and animated, respectively. The stimuli in tasks 3 and 4 were 4º in size and each were non-animated and animated, respectively. Examples of the stimuli used for each task are illustrated in Figure 4.3 and Figure 4.4. The animated stimuli used in this pilot study were downloaded from www.picgifs.com. Ten different stimuli were presented in the centre of the screen in each task, and each stimulus was presented for 3 seconds. The tasks were presented in a random order for each participant to avoid any learning effect.

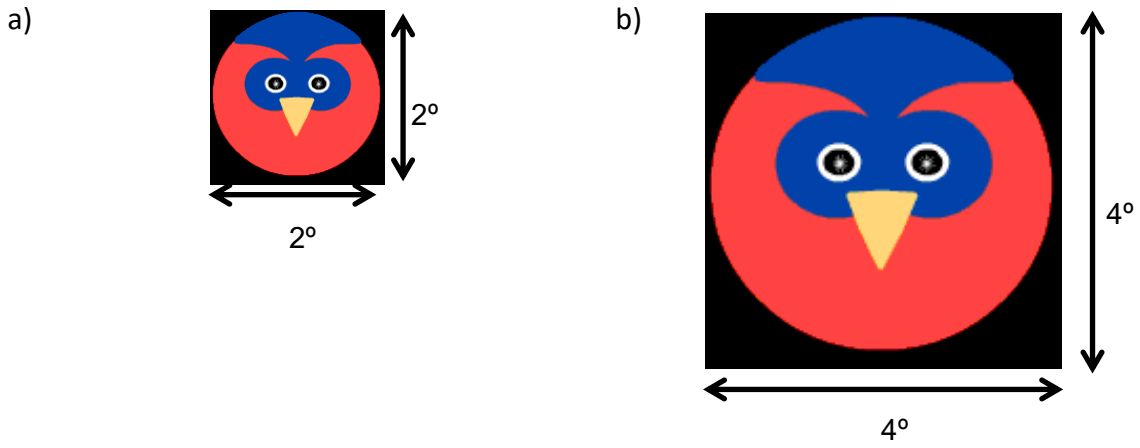


Figure 4.3 Example of a non-animated stimulus used in Task 1 (A) and Task 3 (B) subtending 2º and 4º of visual angle at 65 cm, respectively

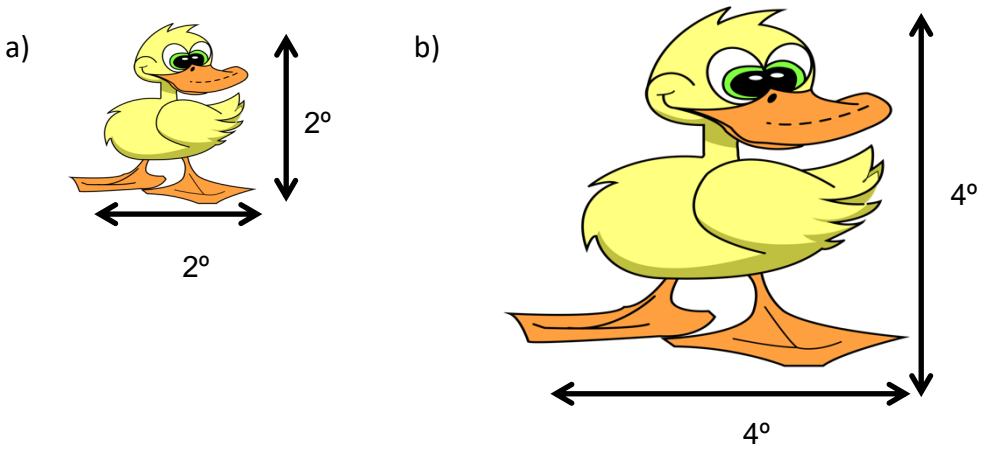


Figure 4.4 Example of an animated stimulus used in Task 2 (A) and Task 4 (B) subtending 2º and 4º of visual angle at 65 cm, respectively. The head of the duck turns left and right and repeatedly, while the wing flaps up and down

4.2.3 Analysis

Raw data containing the eye tracker timestamp in microseconds and the x- and y-position of the right and left eye in pixels were exported from the Tobii Studio™ software into an Excel document. The analysis of the data exported was performed using MATLAB (The Mathworks, Inc., Natick, MA, USA). The data were first cleaned to remove artefacts and filter noise as explained in Chapter 3, section 3.4.2. The eye positions were then converted to visual angles in degrees.

A heat map of the x- and y-position of each eye for each participant and each task was created to visualise the data obtained. A histogram plot was used to determine the probability of the horizontal and vertical eye positions and is visualized in a two-dimensional surface (Figure 4.5). Previous studies have used bivariate probability density functions (PDFs) to investigate the variability of eye position in typical adults (Cherici et al. 2012). A recent study by McIlreavy (2016) also applied PDFs to analyse fixation and smooth pursuit eye movement performance in adults with IN.

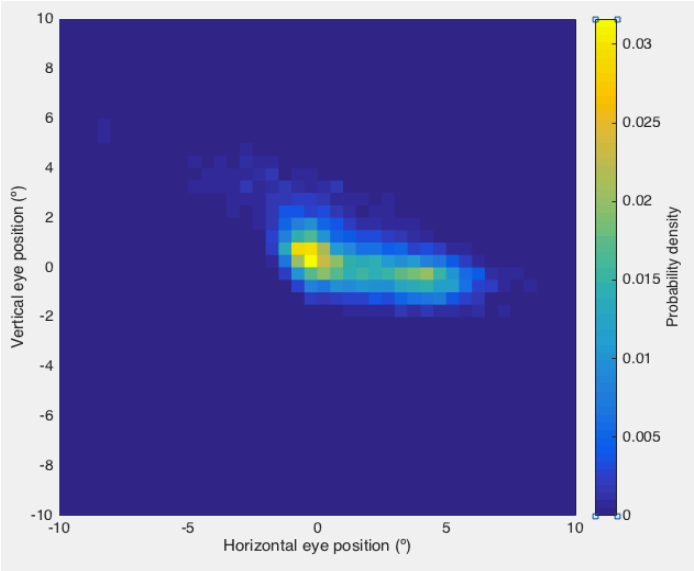


Figure 4.5 Example of a heat map of the x- and y- eye positions of a participant with IN

Routinely, the variability of eye position is quantified by identifying the area in which at least 68% (equivalent to the mean ± 1SD of the normal distribution) of fixations occur (Crossland and Rubin 2002; Bellmann et al. 2004; Crossland, Culham and Rubin 2004; Cherici et al. 2012). The area covering 68% of fixation positions was then calculated. The bigger the area, the less precise the eye movements were. Dr Lee McIlreavy generously provided the codes for this analysis.

Statistical tests were performed using IBM© SPSS© Statistics software version 26 (IMB SPSS Inc., Chicago, IL, USA). Two-Way Repeated Measures ANOVA was applied to compare the means of the total areas of eye position between the different category of tasks in the two groups of participants. A p-value of less than 0.05 was considered as statistically significant.

4.2.4 Results

Six adults with IN (6 males; mean age 40.67±16.78 years) and 6 normally sighted adults (3 males; mean age 27.5±2.88 years) took part in the experiment. All of the adults with IN had visual acuity (VA) better than 0.7 logMAR binocularly. Monocular VA was equal in both right eye and left eye for all of the adults with IN (>0.56 logMAR) except one who had VA of 1.4 in the RE and 0.7 in the LE. The adults in the control group all had visual acuity of 0.00 logMAR or better, monocularly and binocularly. The mean VA for both groups of participants is tabulated in Table 4.1.

Group	**Visual Acuity (logMAR) (mean±SD)**		
	RE	**LE**	**BE**
Adults with IN	0.45±0.51	0.37±0.28	0.32±0.3
Normally sighted adults	-0.14±0.08	-0.15±0.11	-0.02±0.14

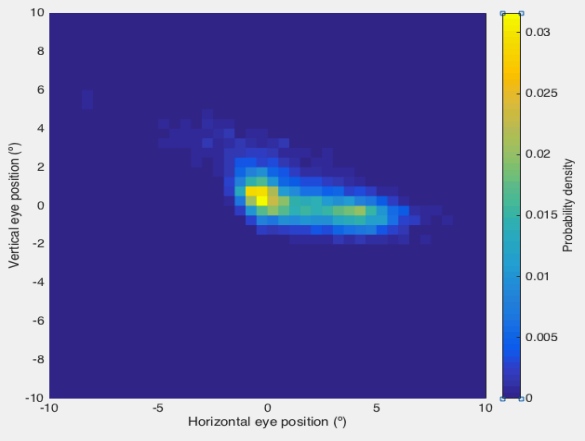
Table 4.1 Mean and standard (SD) of monocular and binocular visual acuity for both groups of participants

A summary of the mean and standard deviation for the total area of eye positions is shown in Table 4.2. Overall, adults with IN produced a larger area of fixations compared to normally sighted adults. The largest area of fixations was seen when the 4º animated stimulus was used in both adults with IN (4.00 deg^2 ± 2.59 deg^2) and normally sighted adults (0.63 deg^2 ± 0.21 deg^2). The smallest area of fixation was seen when the 2º non-animated stimuli was used, also in both adults with IN (3.36 deg^2 ± 4.18 deg^2) and normally sighted adults (0.08 deg^2 ± 0.13 deg^2). Examples of the 2D histogram plots of horizontal and vertical eye positions of the RE of an adult with IN and a normally sighted adult is illustrated in Figure 4.6 and Figure 4.7, respectively.

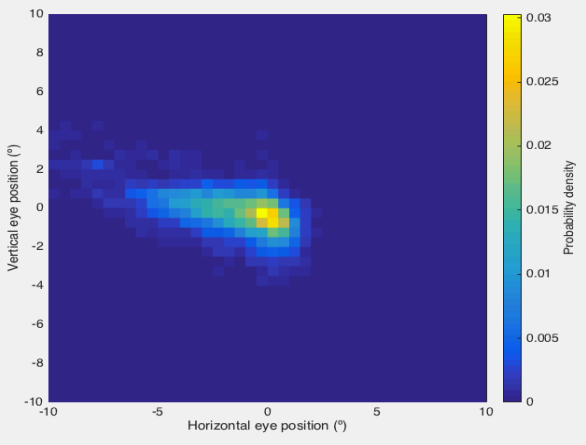
		Total area of eye position (deg^2) (mean±SD)			
		Non-animated stimulus 2º	**Animated stimulus 2º**	**Non-animated stimulus 4º**	**Animated stimulus 4º**
Adults with IN	RE	2.08±1.29	1.46±0.99	1.85±0.96	4.00±2.59
	LE	2.41±1.28	3.04±2.96	3.05±2.42	3.83±2.73
Normally sighted adults	RE	0.17±0.13	0.30±0.11	0.29±0.25	0.63±0.21
	LE	0.21±0.10	0.55±0.27	0.25±0.00	0.79±0.37

Table 4.2 Mean and standard deviation (SD) of the total area of eye positions isocontour (º) in adults with IN and normally sighted adults, expressing the precision of the fixation for right (RE) and left (L) eye

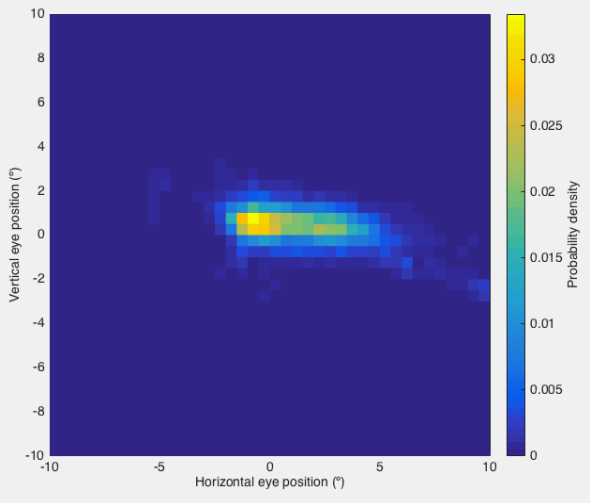
a)



b)



c)



d)

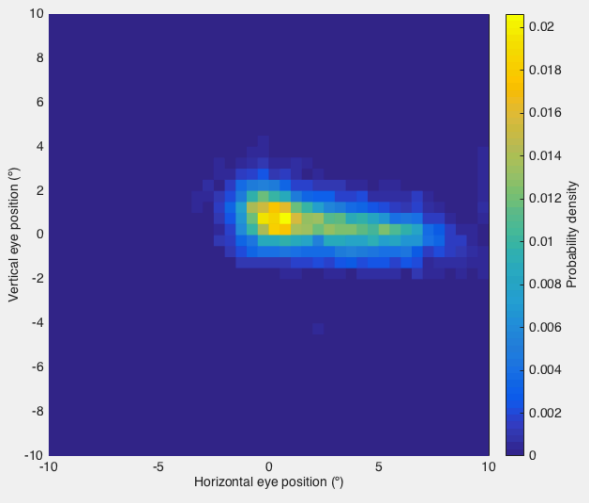


Figure 4.6 2D histogram plots of horizontal and vertical eye positions of the RE of an adult with IN: a) Non-animated stimulus (2º), b) Animated stimulus (2º), c) Non-animated stimulus (4º), d) Animated stimulus (4º)

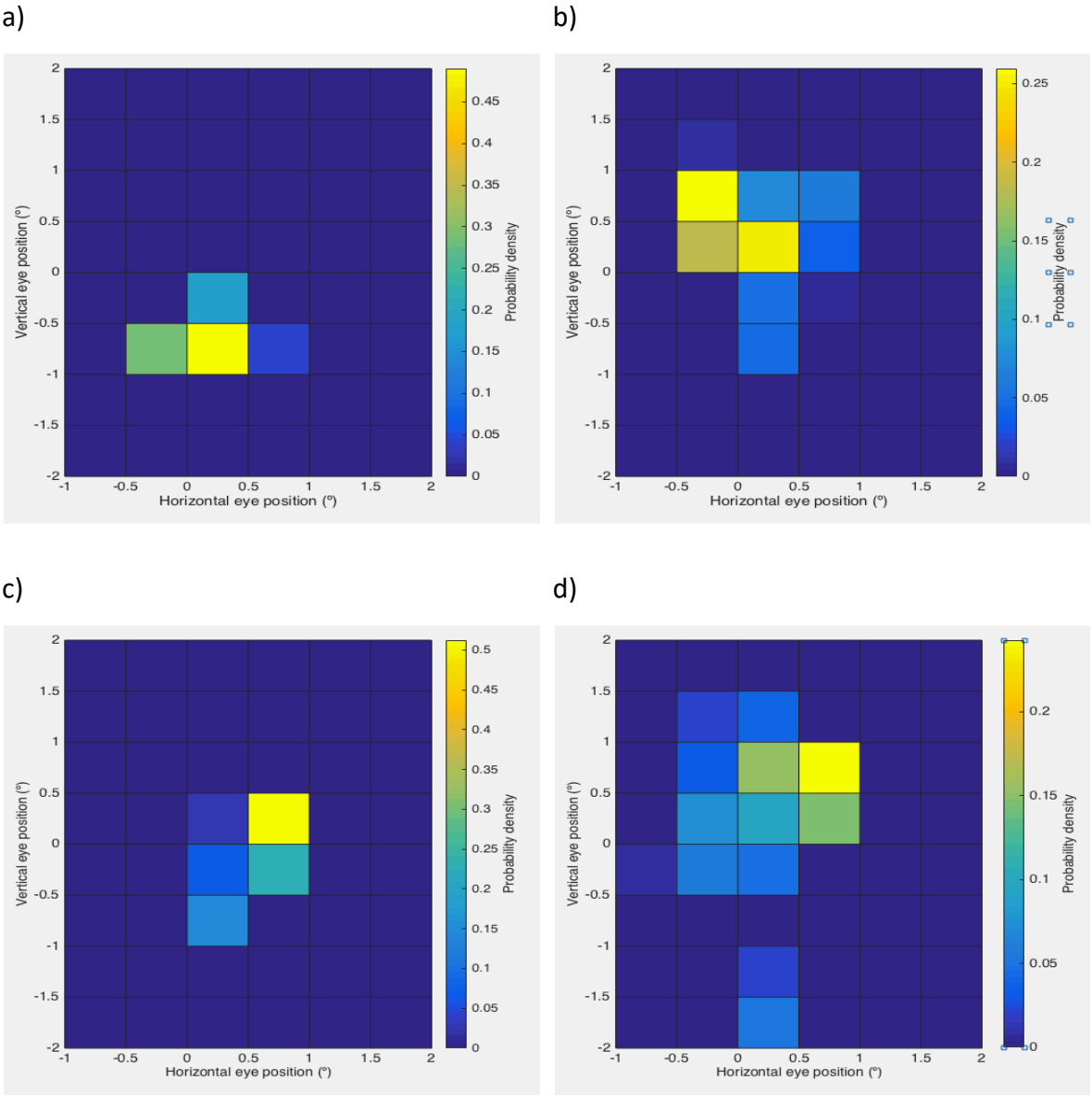


Figure 4.7 2D histogram plots of horizontal and vertical eye positions of the RE of a normally sighted adult: a) Non-animated stimulus (2º), b) Animated stimulus (2º), c) Non-animated stimulus (4º), d) Animated stimulus (4º)

4.2.5 Discussion

As expected, the mean total area of eye positions in people with nystagmus is greater than normally sighted adults. This is almost certainly due to the involuntary movement of the eye.

All horizontal and vertical eye positions from the fast phase and the slow phase of the eye movement were used during the analysis of this experiment. The purpose of using all of the eye positions in the nystagmus waveform was so that there would be more data points compared to if only the fast phases were used (i.e end of saccades), giving us a better picture of where the eyes were while fixating on the stimulus. The large amplitude of nystagmus will produce a larger range of eye positions detected by the eye tracker, therefore resulting in the larger area of fixation. Nonetheless, no significant difference was found in the total area of eye positions between stimulus sizes and types in people with nystagmus, indicating that the different stimulus type and size will produce a similar eye movement performance. Therefore, the use of larger stimuli with more detail would not induce more eye movements within the stimulus area.

4.3 Challenges of eye movement recordings of children with nystagmus with and without DS

4.3.1 Cooperation

Children have short attention span, which can make EMR a challenge. In addition to that, the children often experience fatigue after going through a clinical eye examination prior to the recording, which lasts between 30 to 45 minutes. These two factors can lead to the children being un-cooperative during the EMR. Therefore, a break was given to the children after the eye exam to allow the children to recuperate before beginning the EMR procedure, giving a higher chance of the children cooperating. It must be kept in mind that a large group of children taking part in this study are either children with DS or typically developing children with nystagmus. Therefore, the EMR tasks (i.e. fixation and SP) in this study were designed to be short. Saccadic task was not attempted in this study, as such task requires repetition of multiple saccadic amplitudes, which takes longer than the fixation and SP task (Vinuela-Navarro 2015).

4.3.2 Pre-calibration

As discussed previously, eye trackers are pre-calibrated before proceeding with the recording. However, pre-calibration was not possible for some children. Repeating the pre-calibration procedure multiple times would cause frustration and loss of attention. Therefore, to enable the proceeding of the EMR in children who could not be pre-calibrated, the eye tracker was first pre-calibrated with the researcher's eyes. The EMR data was then calibrated retrospectively using the methods described in Chapter 5, section 3.6.

4.3.3 Monitoring and control of head movement

Typically, a head and chin rest would be used to restrict head movement and maintain viewing distance during EMR. This method would be easy to apply in older typical children. However, younger children and children with special needs often do not like their head restrained. Therefore, I did not use a chin rest during the recordings. As mentioned earlier in the chapter, the Tobii TX300 enables eye tracking with relatively head free head movement. However, the eye tracker has a limit for the head movement, where at least one eye has to be visible within an area of 37cm width by 17cm height, at the distance between 50 and 80cm, and with a maximum head movement speed of 50cm/s. Any movements outside of these dimensions would result in loss of tracking.

One of the conditions that caused the eye tracker to lose tracking is a face turn. This condition occurred frequently in children with nystagmus, as they may have an adopted head position such as a face turn or head tilt to place the eyes in the null position. Face turns can cause one of the eyes to be blocked by the nose bridge, and therefore prevent the infrared illumination from reaching the eye, causing loss of data. However, the eye tracker should be able to pick up the eye that was not blocked by the nose. In this condition, the data chosen will be the eye that was detected by the eye tracker and has more samples. Head tilts were a bit more complicated to handle. When the head was tilted back, the eyelids went down covering parts

of the pupil and hence blocking the infrared light from reaching the pupil. This was overcome by adjusting the eye tracker height or tilt. The head position could also be adjusted, with the researcher or the parent gently restraining the participant's head (Figure 4.8). However, doing this can become a distraction, as most of the children do not like their head to be held, which leads to loss of attention.

a) b)

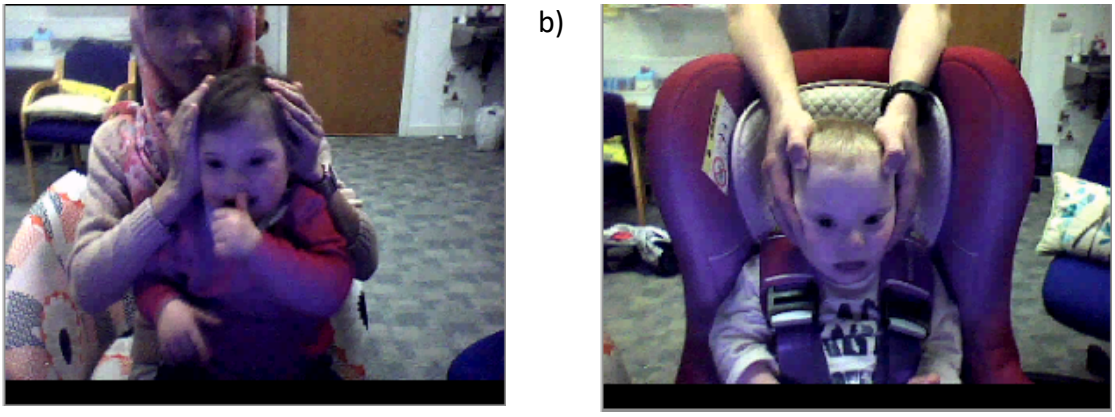


Figure 4.8 Example of participants' head being restrained by the researcher (a) or by the parent (b)

Initially, the participant's head position and movement was monitored using the track status that was available in the Tobii Studio. A new monitoring software (Tobii Pro Eye Tracker Manager, Tobii® Technology) was provided by the Tobii representative later in the study for better monitoring of the eye position and distance from the eye tracker. The software provided a live feed of the track status, compared to the previous track status, which only showed the eye positions at certain samples. The software also provided information on the actual position of the eyes from the eye tracker, whether they were too high or low, far from or close to the eye tracker. The researcher could then make the adjustments accordingly.

4.3.4 Poor quality EMR data

Despite making all the adaptations possible to gain and maintain the attention of the participants in this study, there was still a large amount of poor quality data which could have been caused by one or a combination of the following:

4.3.4.1 Pupil size

The ability of the tracker depends partly on the pupil size. According to the eye tracker developer, the maximum pupil size that can be detected by the eye tracker is 9mm. A pilot experiment was conducted to determine the maximum pupil size the Tobii TX-300 eye tracker was able to track. The experiment was conducted on two adults, one with light coloured and one with dark coloured irides. EM recording was performed binocularly using the fixation test developed by Vinuela-Navarro (2015) on the Tobii Studio system. Baseline pupil size and eye movements were measured and recorded before dilating the subject. During this procedure, the subjects were asked to fixate on the stimulus that was presented at the centre of the screen for 5 seconds. One drop of Tropicamide 1% was then instilled in both eyes. Pupil size and eye movements were then measured and recorded again after one minute of instillation and repeated at 1-minute intervals until the eye tracker was not able to pick up the subject's eyes. At this point, the pupil size was measured using a ruler. The eye tracker was able to record the eyes of both subjects until the pupil size was 5.5mm and 6mm in the two subjects, respectively. Figure 4.9 illustrates the data quality of the eye tracker as the pupil size changes over time in the adult with light coloured iris. Based on this pilot experiment, the maximum pupil size that can be detected by the eye tracker in a light-coloured iris was less than 5.5mm, whereas the eye tracker was able to detect the eye with dark coloured iris up to 6mm of pupil size.

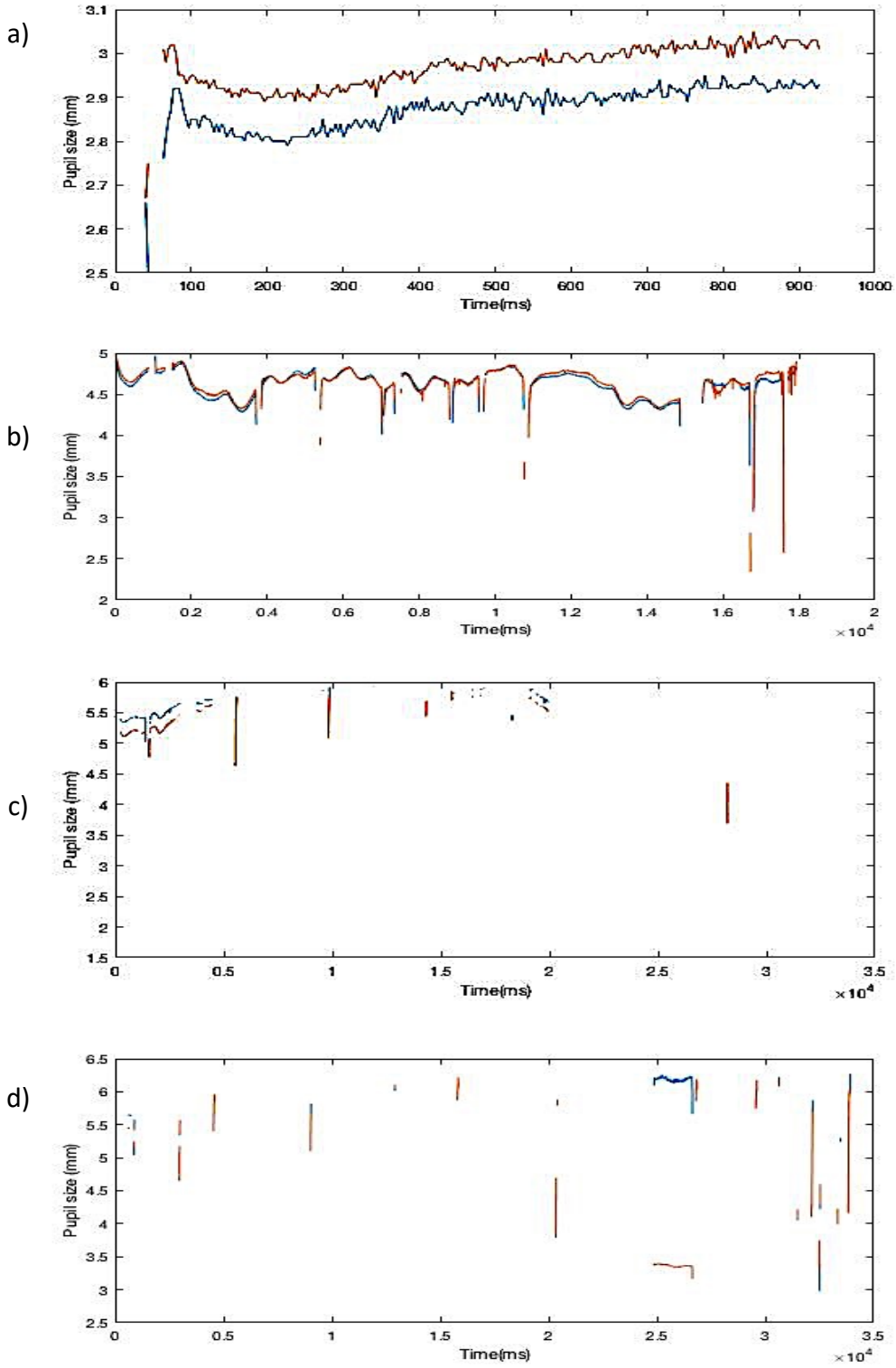


Figure 4.9 Example of eye tracking data while pupils were between a) 2.8-3mm, b) 4.5-5mm, c) 5-5.5mm and d) 6mm of a participant with light colour iris

4.3.4.2 Background colour of task

The background colour of the tasks presented to the participants in this study was initially black. The reason for using black was to make the stimulus stand out and better attract the attention of the children. In most of the children, there was no problem with the data quality when using black background. However, in some of the children, the eye tracker was having difficulties detecting the eyes when the black background was used but was able to track the eyes adequately when a white background was used. It was suspected that the increased luminance of a white vs black background caused the pupils to constrict, hence enabling the eye tracker to better detect the eyes. This factor was only discovered in the later period of the study, so later EMR was performed using white backgrounds on children who were unable to produce good quality EMR data with the black background.

4.3.4.3 Spectacle reflections

As discussed in Chapter 2, children with nystagmus with and without DS often have high prescriptions. Children with DS without nystagmus have also been shown to have high prescriptions (Cregg et al. 2003; Ljubic et al. 2011; Ljubic et al. 2015). The refractive error of the children who participated in this study ranged from -15.00DS to +8.50DS. High prescription spectacles often produce reflections from the screen, which hampers the infrared light from eye trackers in reaching the surface of the eyes. This causes loss of tracking or poor-quality data. Attempts were made to adjust either the tilt of the spectacles or the eye tracker to remove the reflections from the plane of the infrared light. In cases where the adjustments did not work, EMR was performed without the spectacles. Previous studies have shown that uncorrected refractive error does not affect pursuit performance (Dell'Osso and Jacobs 2013).

4.4 Success rate of eye movement recording

Despite the steps taken to overcome the challenges of EMR discussed above, the success rate of EMR in children with nystagmus with and without DS was still poor. A total of 10 children (7 DSN, 2 DS, 1 T) returned for re-recording after the problems were identified and 6 recordings were successful. As already mentioned, the short attention span of children can present a challenge to eye movements recording. Throughout the study, a total of 85 children (28 DSN, 20DS, 17TN and 20T) were seen. Of this, good quality EMR data was obtained from 51 (60%) children (11DSN, 10DS, 10TN, and 20T). The data presented in the main experiments of this thesis in Chapters 6 and 7 are based on these children.

4.5 Summary

In this chapter, animated stimuli with facial features of animals were designed and tested to attract the attention of young children during EMR. The quality of EMR data in adults with and without nystagmus while fixating on two different stimulus types (animated and non-animated) and sizes (2º and 4º) were compared by looking at mean the total area of eye positions between the two groups. There was no significant difference between the mean total area of eye positions between both stimulus types and sizes for both adults with and without nystagmus. Therefore, using big animated stimuli should not affect the quality of EMR data in future experiments. However, there were challenges that contributed to poor quality EMR data, resulting in low success rate in children with nystagmus with and without DS. The challenges faced included inability to pre-calibrate eye tracker before performing EMR tasks, head and face turns, pupil size and spectacle reflections. Although the adjustments made did improve in the EMR data quality, success rate was still low in DSN, TN and DS group of children. Nonetheless, this study demonstrates that EMR recording was feasible in young children with nystagmus and special needs (DS).

CHAPTER 5 RETROSPECTIVE CALIBRATION OF EYE MOVEMENT RECORDING DATA

5.1 Introduction

Usually, participants undergo a calibration procedure immediately prior to any eye movement recording. Pre-calibration of the Tobii TX300 requires the participant to look at a number of targets which are displayed sequentially at known locations on the screen as described in Chapter 3, section 3.4. An acceptable calibration would require the eyes to be stable while fixating on the targets displayed. However, individuals with nystagmus are not able to fixate steadily, so producing poor calibration, requiring the calibration procedure to be repeated. Repeating procedures on child participants is unlikely to be successful, as it causes frustration, leading the child to lose interest in the task itself and subsequent tasks. Many studies investigating nystagmus in infants and young children do not calibrate the EMR data (Hertle and Dell'Osso 1999; Hertle et al. 2002). However, calibration of EMR data is important to obtain precise analysis of the eye movement performance. Recent studies have come up with methods of calibrating EMR data retrospectively using smooth pursuit data or saccadic main sequences (Jones et al. 2013; Theodorou et al. 2015). Calibrating the EMR data retrospectively would be a more appropriate method of calibration, allowing the researcher to proceed with the EMR while maintaining the child's cooperation and subsequently obtaining precise analysis of eye movement performance. Therefore, in this chapter we explain the validation of retrospective calibration performed using smooth pursuit EMR data of adults with and without nystagmus.

5.2 Methods

EMR was performed on an adult with nystagmus and an adult with no nystagmus using the method described in Chapter 3 section 3.4, while the participant performed a smooth pursuit

task. The experiment involved the participants performing two repetitions of the smooth pursuit task that is described in section 3.4.2. The first time, EMR was performed using the participant's own pre-calibration (hereby known as "pre-calibrated" data) followed by EMR performed using pre-calibration of another participant (hereby known as "un-calibrated" data). EMR data output as described in Chapter 3, was then exported from Tobii Studio and imported into MATLAB for analysis.

5.3 Retrospective calibration of pre-calibrated non-nystagmus data

The data, again, were first cleaned to remove artefacts and filter noise. The cleaned data of the RE were then used for the retrospective calibration procedure. All data before the task begins and after task ends were removed, leaving only data when the eye was performing the SP task (Figure 5.1). Data of the first ramp of the SP task were then extracted from the whole data set. During the initiation phase of smooth pursuit eye movement, the eyes does not move when the target begins to move for a period between 100 and 130ms, known as latency (Barnes 2011). Additionally, participants may anticipate the stimulus stopping or changing direction and slow their eye movements at the end of a ramp. Therefore, the first and last 125 data points were removed from the extracted data, to avoid the effect of the latency and reversal artefacts on the calibration process. The eye position (EP) data in pixels vs target position in degrees were then plotted and a line fitted through the data points (Figure 5.2), producing a slope and intercept value of the fitted line. In this example, the slope and intercept value was 43.62 pixels/º and 875.14 pixels respectively.

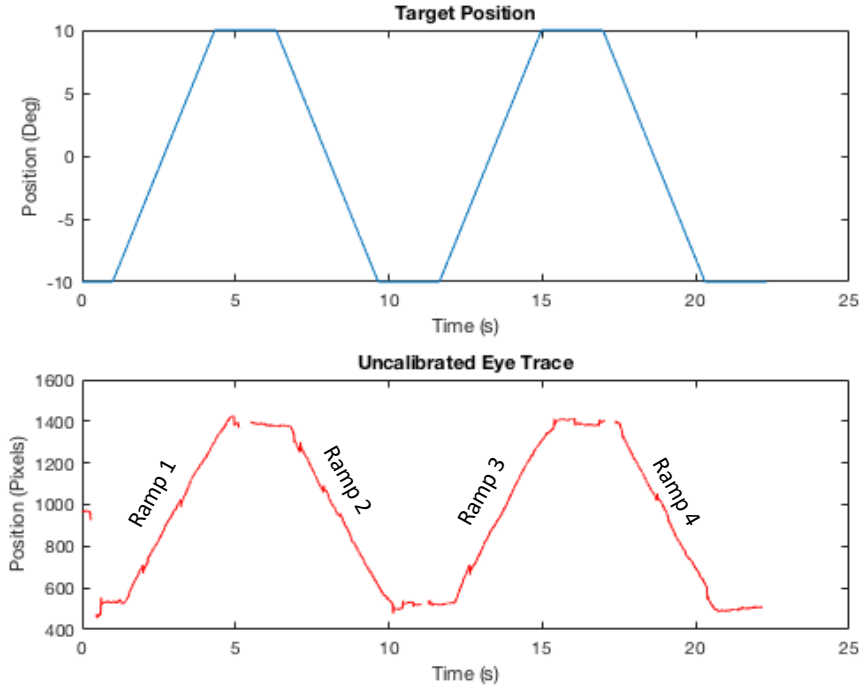


Figure 5.1 (a) The trajectory of the target was trapezoidal, with 4 sweeps (ramps) of 2s of motion at 6°/s across 20° punctuated with 2s of fixation, and (b) the corresponding un-calibrated eye movements from a non-clinical adult participant

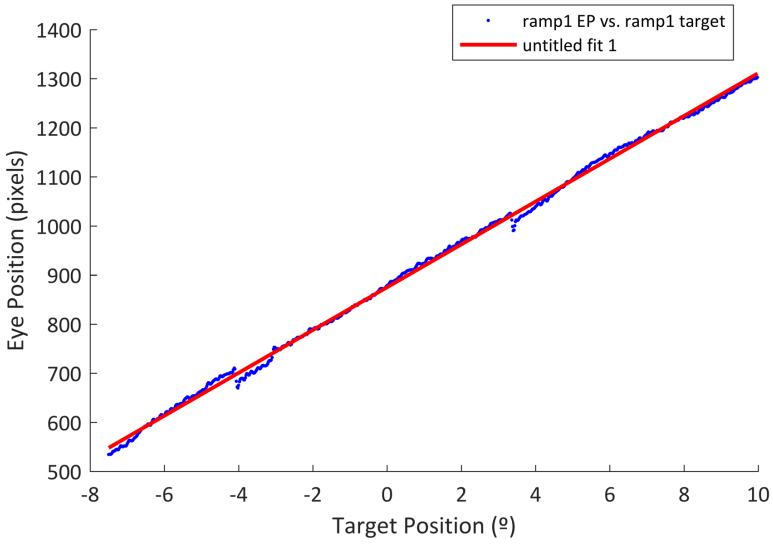


Figure 5.2 Eye position (pixels) plotted against target position (degrees) for the rightward ramp of smooth pursuit shown in Figure 5.1. The linear fit (y=mx+c) is shown as a solid red line. In this example, the slope and y-intercept were 43.62 pixels/° and 875.14 pixels, respectively

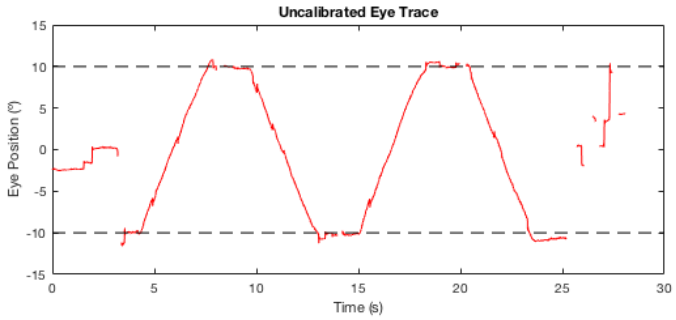
The whole cleaned EP data in pixels data were then calibrated to produce a new set of EP data in degrees using the formula:

$$x = \frac{y - c}{m}$$

where,
x = newly calibrated EP in degrees
y = known eye EP obtained from the fitted line
c = intercept value obtained from the fitted line
m = slope value obtained from the fitted line

A plot of the un-calibrated and calibrated eye trace was created (Figure 5.3). Since these EMR data were pre-calibrated with the eye tracker with a good calibration, no change was seen in the amplitude of the SP, which was 20º (i.e. the correct amplitude was successfully generated). However, the EP seems to shift approximately 2º to the right. The procedure was repeated using the second SP ramp for calibration. This time, the calibrated data shifted toward the left by approximately 2º (Figure 5.4).

a)



b)

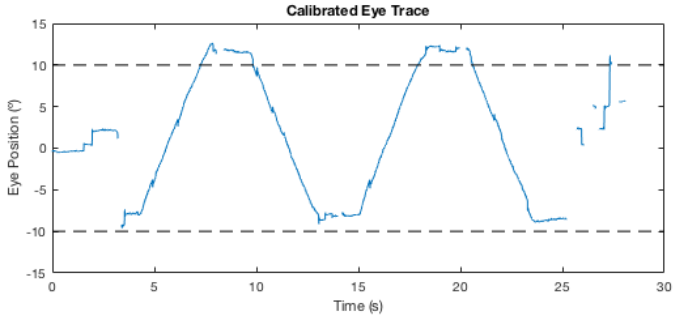
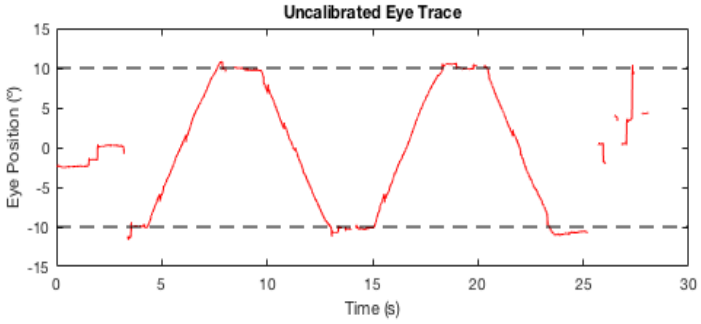


Figure 5.3 a) The uncalibrated eye positions and b) the eye positions being calibrated retrospectively using the first ramp (rightward sweep) of the SP task

a)



b)

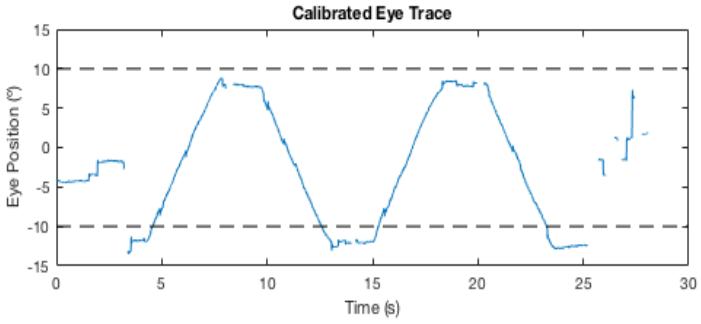


Figure 5.4 a) The uncalibrated eye positions and b) the eye positions being calibrated retrospectively using the second ramp (leftward sweep) of the SP task

The shifts observed are caused by positional lag (Shanidze 2016). When the target jumped from 0º to -10º, the eyes were still at 0º and only made a saccade to the -10º position after 0.35 seconds. When the target started to move rightwards at 6º/s, the eyes remained at -10º for 1.3 seconds and then starts to follow the target, as shown in Figure 5.5. Figure 5.6 shows the graph of EP vs target position of the first SP ramp after removing the first 125 samples from the ramp. As seen in this figure, at 2.5 seconds, the target position is at -1º but the EP is -3º, showing that the eye is lagging in position. During the retrospective calibration, I assumed that the eye position is the same as the target position. Therefore, to place the EP on the target position, the EP data were shifted upwards (i.e. rightwards) as shown by black arrows in Figure 5.6. The same process occurred when the calibration was performed using ramp 2 of the SP task. Figure 5.7 shows the EP data (red line) is above the target position (blue line) indicating that the eye is lagging behind the target while the target is moving leftwards. In order to place the eyes on the target, the EP data were shifted down (i.e. to the left) causing the whole EP data to be shifted down seen in Figure 5.4.

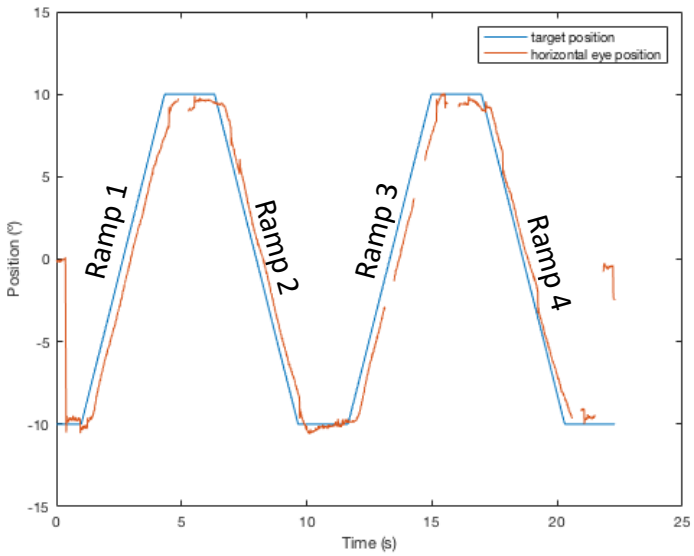


Figure 5.5 Eye position (red line) and target position (blue line) during SP task. The eye position is not superimposed on the target (i.e. shifted to the right) indicating that the eye does not move at the same time as the target (i.e. delayed). The slope of the eye positions matches the slopes of the target position indicating a good velocity gain

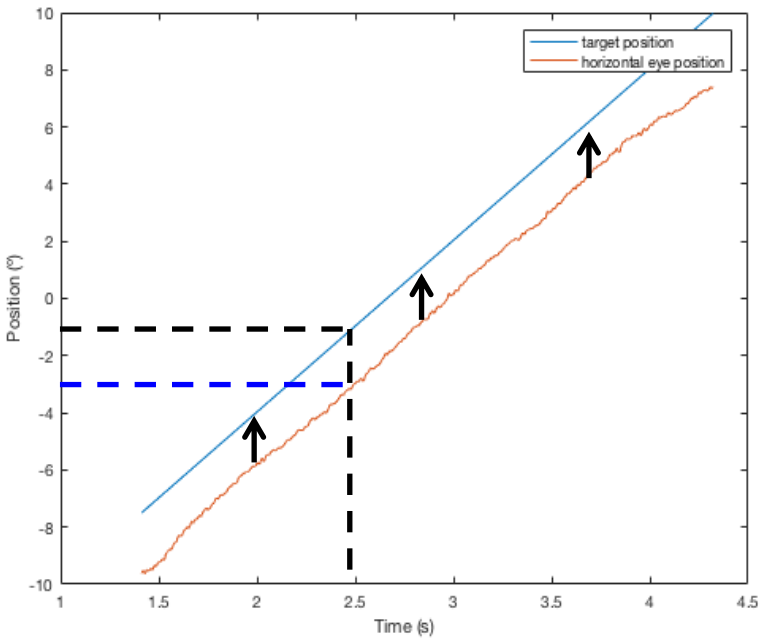


Figure 5.6 Horizontal eye position (red line) vs target position (blue line) of ramp 1 of the SP task (rightward sweep) after removing 125 samples from the beginning of the ramp until target reaches -10º. Black arrows show the direction (upwards) where the horizontal EP data is shifted to match the target position during retrospective calibration

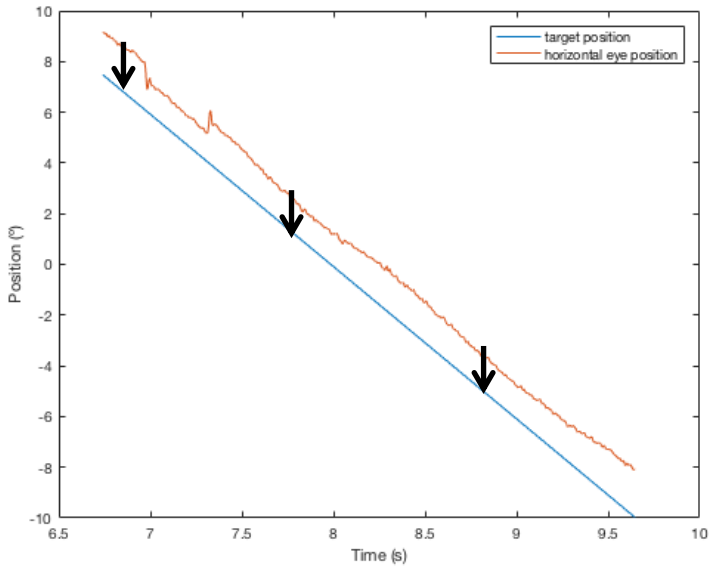


Figure 5.7 Horizontal eye position (red line) vs target position (blue line) of ramp 2 of the SP task (leftward sweep) after removing 125 samples from the beginning of the ramp until target reaches +10º. Black arrows show the direction (downwards) where the horizontal EP data is shifted to match the target position during retrospective calibration.

To obtain the exact EP that was on target, the midway point between the calibrated data from the two ramps was calculated for the whole EP data by obtaining the difference between the two shifts (i.e. calibration with ramp 1 and ramp 2) and dividing by two. Figure 5.8 shows the plot of EP data calibrated with all three methods (ramp 1, ramp 2 and midway). When the midway values were plotted, a graph that is the same as the pre-calibrated eye traces was produced (Figure 5.9).

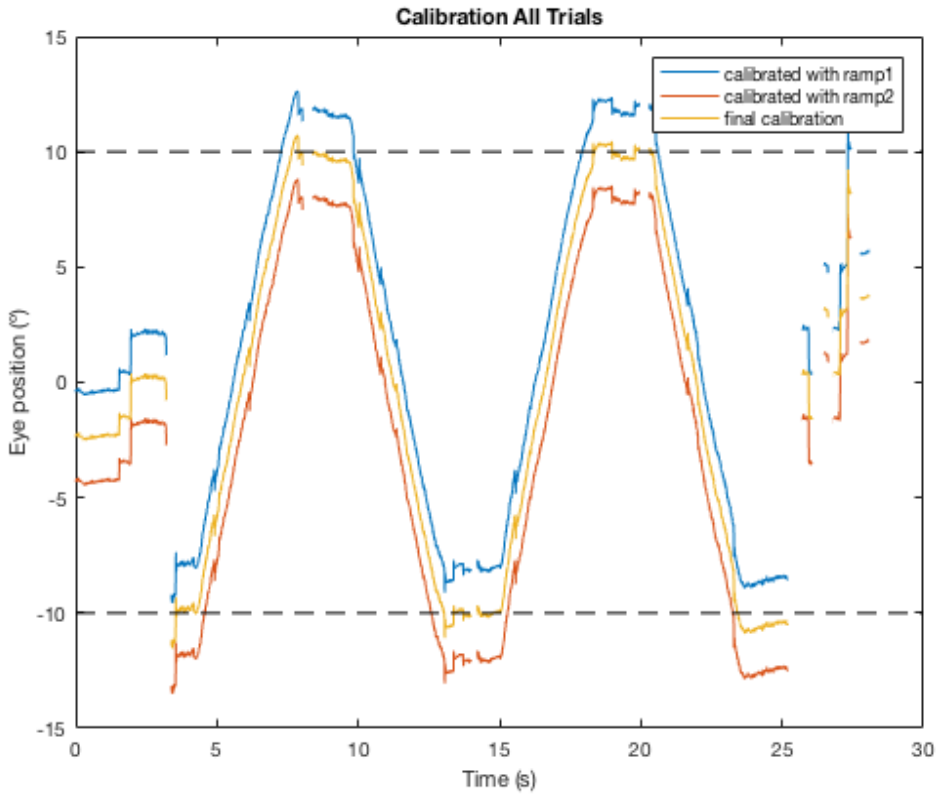


Figure 5.8 Eye position data calibrated retrospectively using the first ramp (blue line), second ramp (red line) and the final calibration (yellow line) which was obtained by dividing the difference between the data calibrated from the two ramps by two

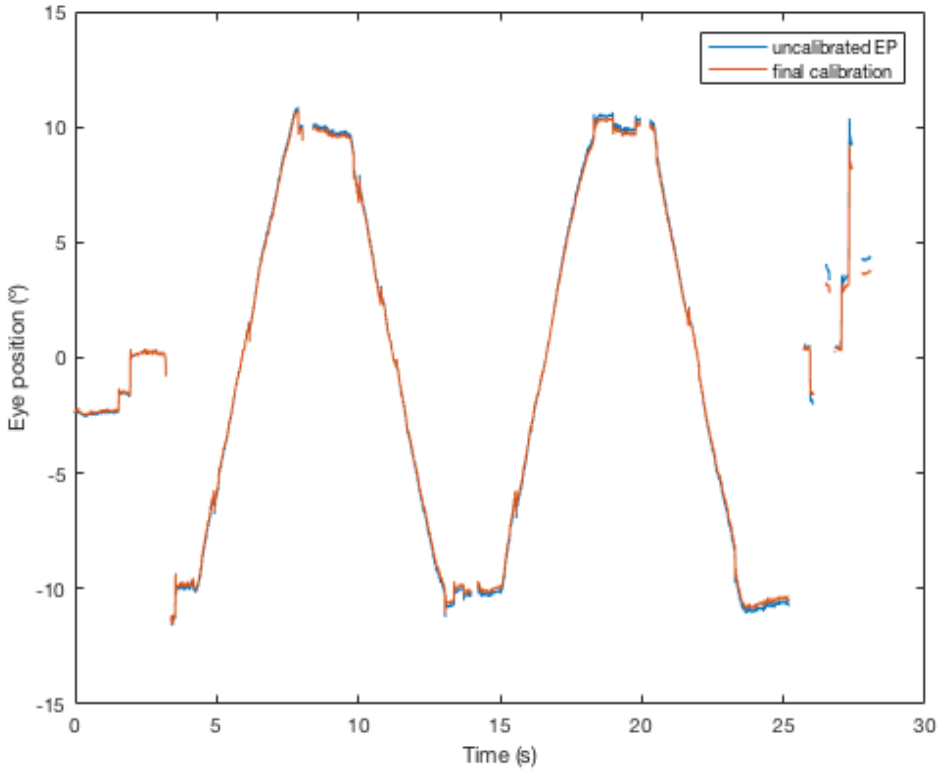


Figure 5.9 The final calibrated eye position data (red line) and the pre-calibrated data are superimposed, indicating that the retrospective calibration produces data similar to that of a good pre-calibrated data by the eye tracker

To determine whether the calibration had affected the SP velocity gain, which is defined as eye velocity divided by target velocity, the gain for the calibrated EP obtained from both ramps and final calibration were calculated and compared to the actual gain from the pre-calibrated data. Results showed no difference between the velocity gain of all four EP data (gain of pre-calibrated data = 1.03, ramp 1 = 1.02, ramp 2 = 1.03, final calibration = 1.02) suggesting that the velocity is the same regardless which ramp is used for the calibration process. Therefore, only good data from a single ramp would be required for the calibration.

5.4 Retrospective calibration of un-calibrated EMR data

The retrospective calibration procedure was repeated on EMR data of the same subject (AZ) using another subject's (AH) pre-calibration on the eye tracker (un-calibrated data). The aim was to show that the retrospective calibration works on un-calibrated data by correcting the amplitude to the actual amplitude. Data of the RE were used for analysis. Figure 5.10 shows the eye trace of the un-calibrated EP and the pre-calibrated EP of subject AZ in pixels.

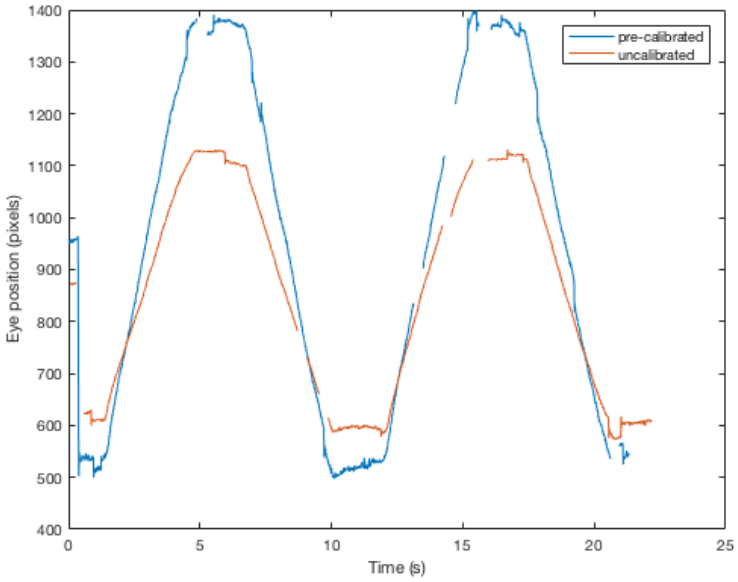


Figure 5.10 Eye position in pixels of subject AZ pre-calibrated with subject AZ (blue line) and subject AH (red line), here referred to as the uncalibrated data. The uncalibrated data has a smaller amplitude despite the task being performed by the same subject

The un-calibrated EP data show the amplitude of the SP task performed by subject AZ was only 13.02º, whereas in fact, we know that the SP amplitude performed was actually 20º. As per the previous experiment, the slope and intercept values were obtained from ramp 1 and ramp 2 of the SP task and used to calibrate the horizontal EP data. Once the EP data were calibrated, the amplitude of the SP task performed subject AZ was stretched to 20º, as it should be (Figure 5.11).

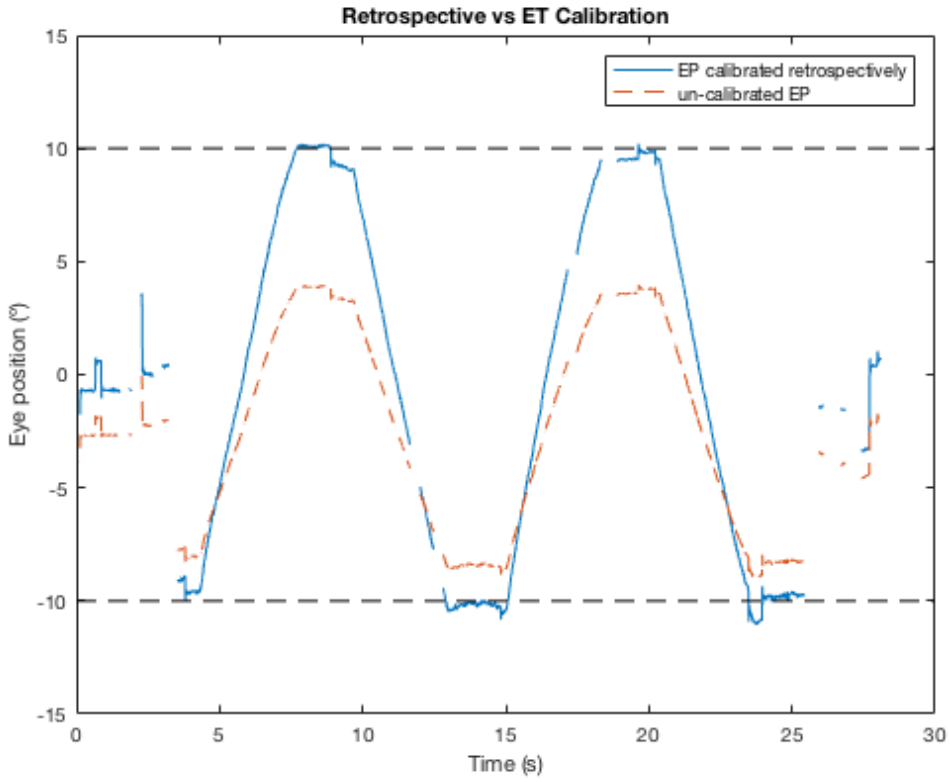


Figure 5.11 The eye position data calibrated retrospectively vs the uncalibrated eye position. The SP amplitude of the calibrated data is stretched to the correct size, 20º

The newly calibrated data of subject AZ were then plotted alongside the previous pre-calibrated EP data of subject AZ (Figure 5.12). The plot shows the newly calibrated EP data superimposed on the pre-calibrated EP data. The velocity gain of the un-calibrated data and newly calibrated data were then calculated. The gain of the un-calibrated data was 0.63, whereas the gain of the newly calibrated was 1.04, which is almost exactly the same as gain of the pre-calibrated data (1.03). This suggests that the retrospective calibration method is reliable in calibrating EMR data that are not properly pre-calibrated by the eye tracker, such as in subjects with nystagmus.

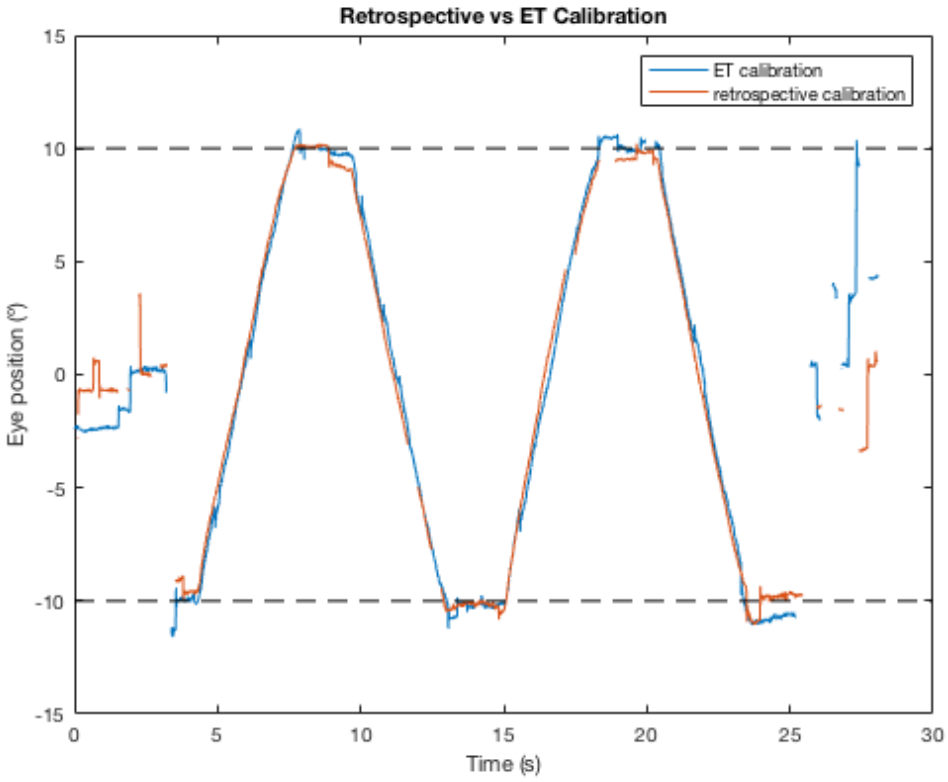


Figure 5.12 Eye position data calibrated retrospectively (red line) and the pre-calibrated eye position data are superimposed, indicating that the retrospective calibration can be applied to data that is not pre-calibrated with the subject's eyes

5.5 Which ramp to use?

The output of an ideal recording would have good quality data from all four SP ramps of pursuit. However, there may be cases in which not all of the SP ramps have good quality data (i.e. a lot of missing data and/or too much noise). In such cases, only the ramp with the best quality data (containing at least 50% of the samples in the ramp) would be used for analysis. The question is, would calibration with different ramps produce the same calibrated data? The following experiment compares the velocity gain of data calibrated with each of the four SP ramps of subject AZ. As demonstrated and explained previously, the calibrated EP data is shifted systematically when using different ramps (Figure 5.13) because of actual latency in moving the eyes. Velocity gain for ramp 1 of EP data calibrated with each of the 4 ramps was

calculated. Data calibrated with ramp 1 showed velocity gain of 1.03, and velocity gain of EP data calibrated with ramp 2, 3, and 4 was 1.04, 0.99 and 0.98 respectively, showing only a very small difference from the velocity gain of the pre-calibrated data (1.03). This demonstrates that any of the 4 ramps can be used to calibrate EP data retrospectively. This result suggests a potential error of only ±2º.

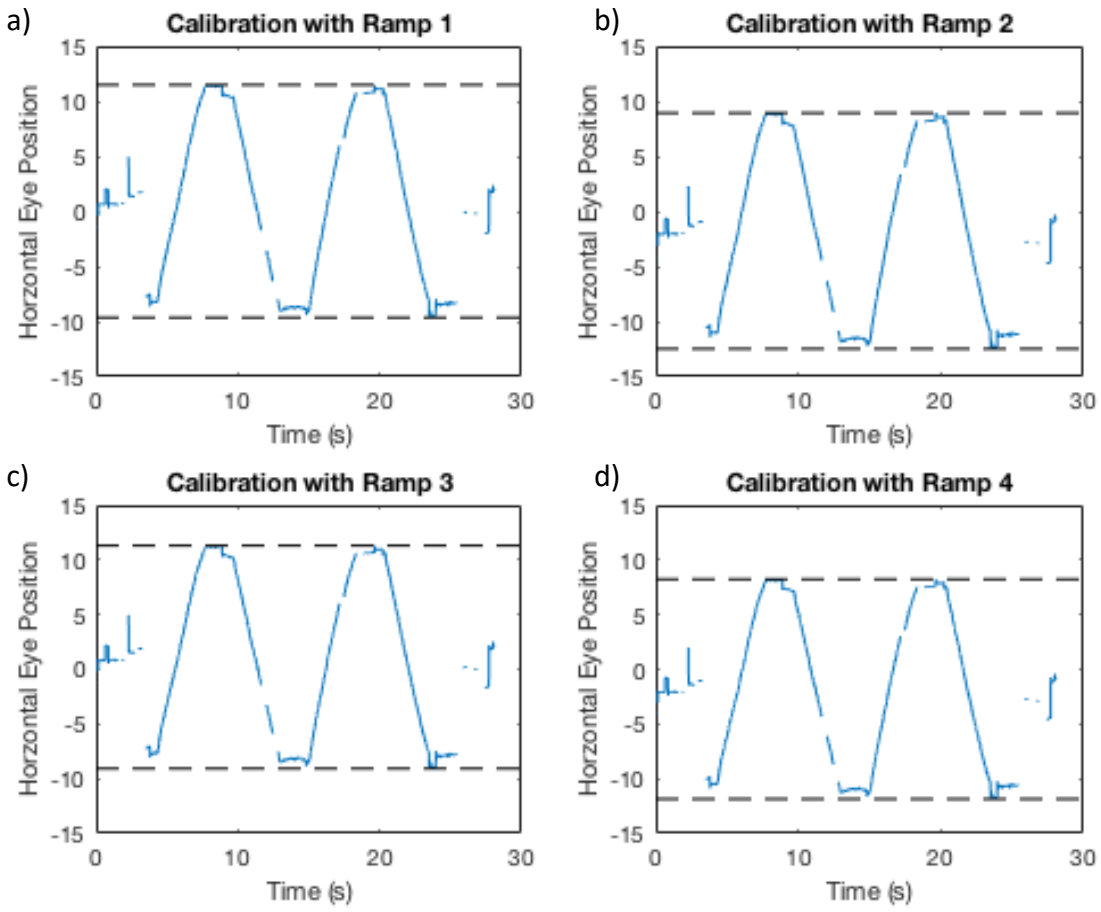


Figure 5.13 Shifts in the eye position data when calibrated with each of the four ramps; a) ramp 1, b) ramp 2, c) ramp 3 and d) ramp 4

To determine the normal variation in gain, pre-calibrated and un-calibrated EMR was performed on 5 typical adults while they were performing the SP task. The un-calibrated data were calibrated retrospectively, and the gains of all four SP ramps were calculated and compared to pre-calibrated data. The mean velocity gains for eye movement data calibrated

with all four smooth pursuit ramps are shown in Figure 5.14. Velocity gains of un-calibrated and pre-calibrated data are also shown in the same figure. This shows that the calibration method using any of the four smooth pursuit ramps will produce a calibrated data that is not significantly different from a properly pre-calibrated data, i.e. repeatable.

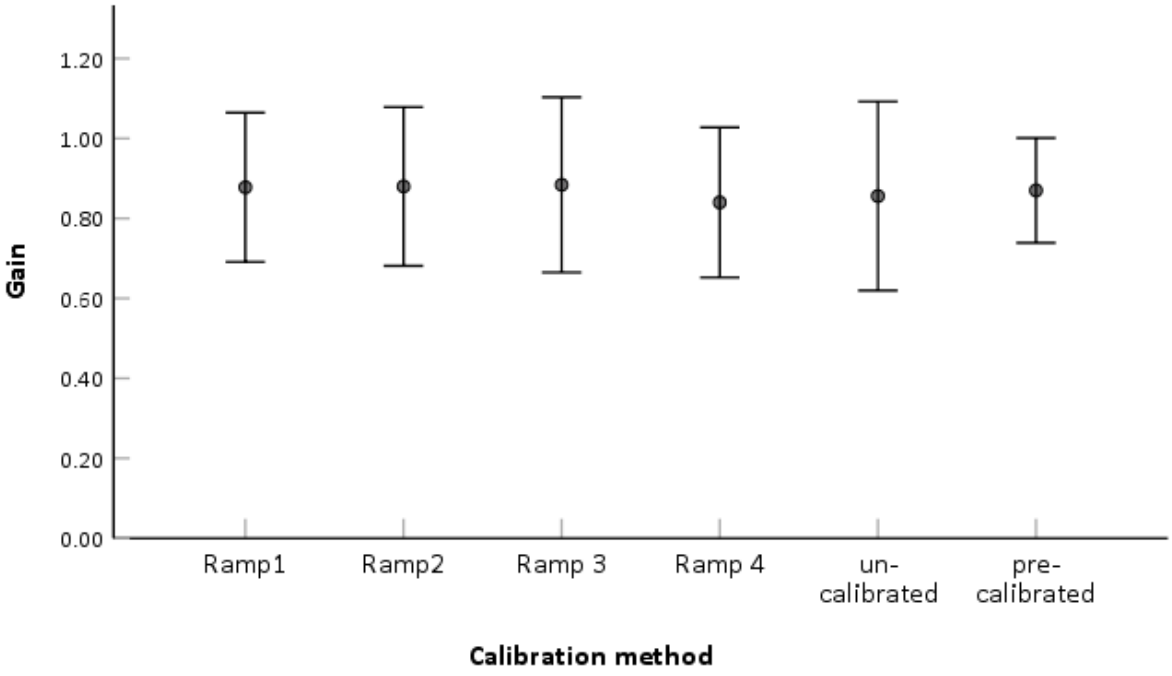


Figure 5.14 Mean velocity gain of eye movement data of 5 typical adults calibrated with each smooth pursuit ramp compared to un-calibrated and pre-calibrated data. Error bars depict 95% confidence intervals

5.6 Retrospective calibration of vertical EP data

The retrospective calibration discussed above applies to the calibration of horizontal EP data since the SP task performed was horizontal. However, to enable two-dimensional measurement of EM, calibration of the vertical EP would also be required. Ideally, data from vertical pursuit should be used to calibrate vertical eye position data. To shorten the duration of the EMR procedure, I did not ask the children in this study to perform vertical pursuit task, so vertical pursuit data were not available. Therefore, I needed to establish whether the retrospective calibration using horizontal pursuit could be applied to vertical EP data. To do

this, EMR of subject AZ was performed using a pre-calibration of a different subject (AH) while looking at a fixation target that jumped vertically from the centre of the screen (0º) to +10º (up), requiring a 10º saccade. The target remained at +10º for 5 seconds, before jumping to -10º (down), requiring a 20º saccade. After remaining at -10º for another 5 seconds, the target then returned to 0º for another 5 seconds, requiring a final saccade of 5º.

Figure 5.15 shows the vertical EP data alongside the target position of the fixation task. The EP is above the target position because of the subject AZ's position, which was higher during the recording, relative to subject AH's position during the pre-calibration. As shown in Figure 5.15, the un-calibrated saccade amplitudes are smaller than the expected saccade amplitudes for the pattern of target motion.

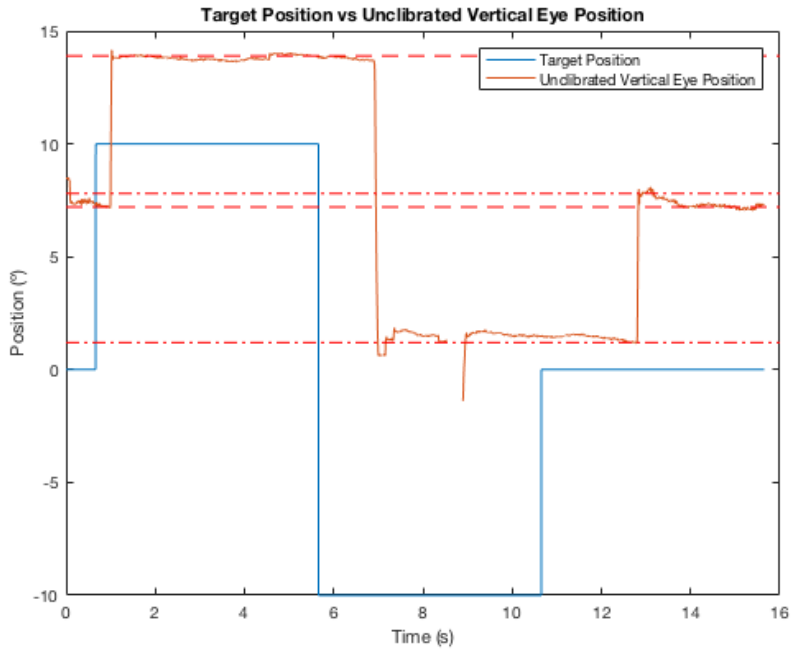


Figure 5.15 The trajectory of the fixation target (blue line), first displayed at the centre of the screen (0º) then jumping up to 10º position vertically then jumping down to -10º, producing a 20º saccade, then returning to 0º producing another 10º saccade, punctuated by a 5s fixation at each position, and the corresponding uncalibrated eye movements from a subject AZ (red line)

The EP data were then calibrated using the same formula (x=(y-c)/m), as explained previously. The slope and intercept values used were obtained from the calibrated data of the horizontal pursuit task. Since we have shown that there is no difference in the velocity gain of the calibrated EP data between all 4 SP ramps, therefore the slope and intercept values of the calibrated data from any of the 4 ramps can be used. In this example, I used the values obtained using the first SP ramp 1 (m= 26.43 and y=827.22).

Figure 5.16 shows the newly calibrated EP data alongside the un-calibrated EP data. As seen in this figure, the amplitudes of the saccades have been stretched from 6.7º up, 13º down and 6.7º up to 10.95º up, 20.75º down and 10.3º up respectively, which is as it should be, as shown when plotted alongside the pre-calibrated EP in Figure 5.17. This indicates that the retrospective calibration using horizontal pursuit can be applied to calibrate EP on both horizontal and vertical axis, allowing two-dimensional analysis of the eye movement data.

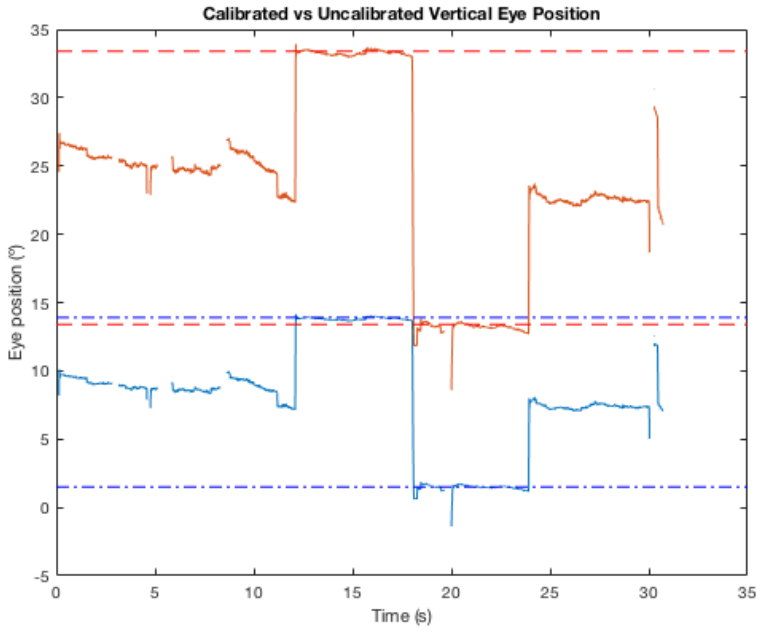


Figure 5.16 Eye position data after retrospective calibration (red line) compared to un-calibrated data (blue line) using the slope and intercept value obtained from the calibration of horizontal calibration

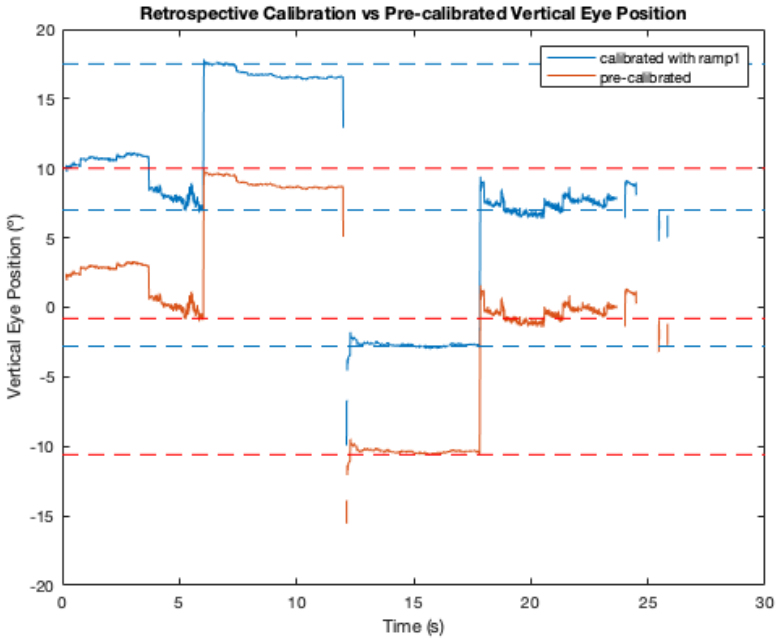


Figure 5.17 Eye trace of eye position data calibrated retrospectively (red line) compared to eye position data pre-calibrated on the eye tracker by subject AZ. The saccade amplitudes of the data calibrated retrospectively is the same as that of the pre-calibrated data (10º, 20º and 10º)

5.7 Retrospective calibration on nystagmus data

We have shown that the retrospective calibration of horizontal and vertical eye movements produces reliable data in a typical adult with no nystagmus. However, nystagmus eye movement data are different from that of a non-nystagmus data, in which both fast and slow phases are involved. Since the main subjects involved in this study are children with nystagmus, therefore, the reliability of the retrospective calibration method needed to be determined for those with IN. Eye movement of an adult with IN performing a SP task using the subject's own pre-calibration (hereby known as "pre-calibrated data") and pre-calibration by a different subject (hereby known as "un-calibrated data") was recorded. The un-calibrated eye movement data (Figure 5.18) were calibrated retrospectively using the methods described in the previous sections and then compared to the pre-calibrated data (Figure 5.19).

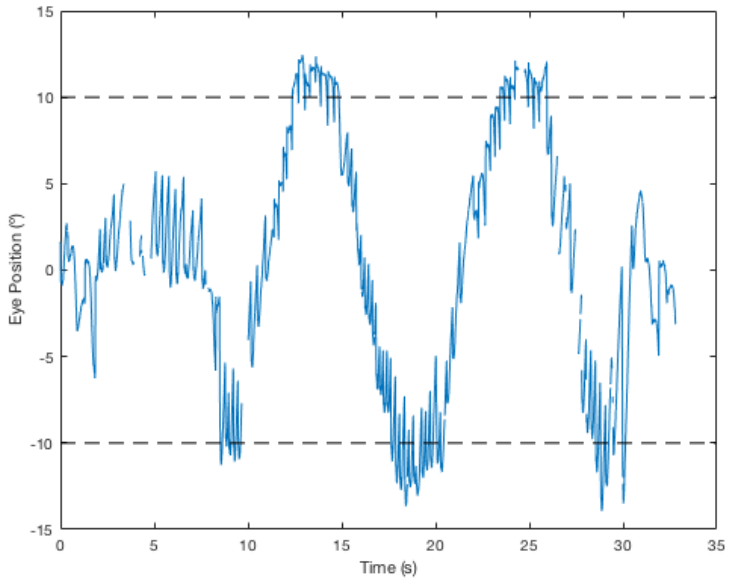


Figure 5.18 Eye trace of un-calibrated eye movement data of an adult with IN performing an SP task

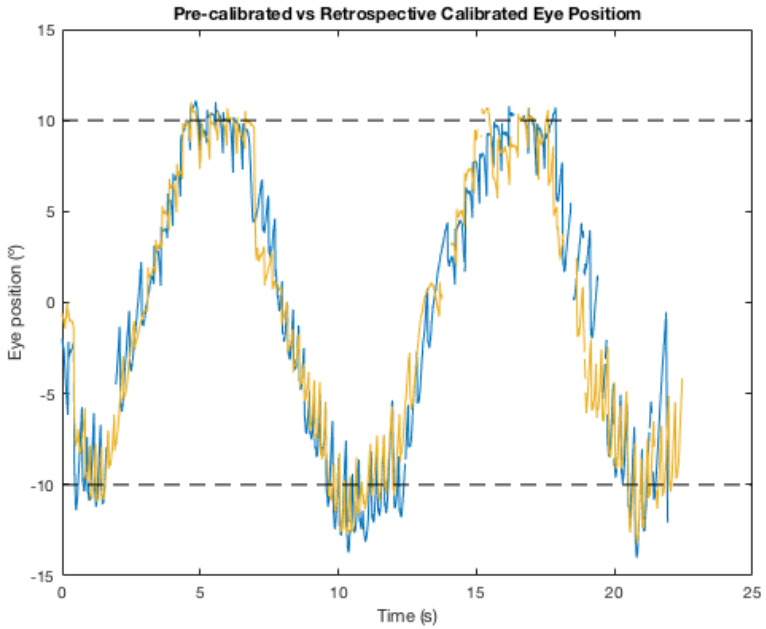


Figure 5.19 Eye movement data of an adult with IN calibrated retrospectively (blue line) and pre-calibrated data of the same adult (yellow line). Dashed lines depict amplitude of SP ramps

The main sequences of the nystagmus fast phases have been shown to follow the typical saccadic main sequence (Abadi and Worfolk 1989) which shows a linear relationship between the amplitude and duration of the saccade (Bahill, Clark and Stark 1975; Garbutt, Harwood and Harris 2001). Therefore, to determine the reliability of the retrospective calibration on nystagmus eye movement data, the amplitude-duration main sequence of the nystagmus fast phases of the calibrated nystagmus data was plotted. The duration of each fast phase is known. If the calibration is unreliable, causing the amplitude of the fast phases to be inappropriate, the data then should not follow the duration-amplitude main sequence. Figure 5.20 shows the fast phases of the nystagmus waveform that were extracted from the calibrated SP task when the subject was fixating at the centre of the screen before the start of the task. A total of 8 fast phases were selected after removing all the dropped data. The duration of the saccades was plotted against their amplitude, producing a saccadic duration-amplitude main sequence (Figure 5.21). A regression line was fitted to the plot to determine the relationship between the duration and amplitude. The slope value obtained was (3.06 ms/º) and the intercept value was (20.39 ms). The range of typical slope and intercept values of the amplitude-duration main sequence in previous publications was (1.5 to 3.10 ms/º) and (20 to 30 ms) respectively (Garbutt, Harwood and Harris 2001). Therefore, the slope and intercept values of the saccadic main sequence obtained from the data calibrated retrospectively in this study fall within published range, validating the retrospective calibration method on nystagmus data.

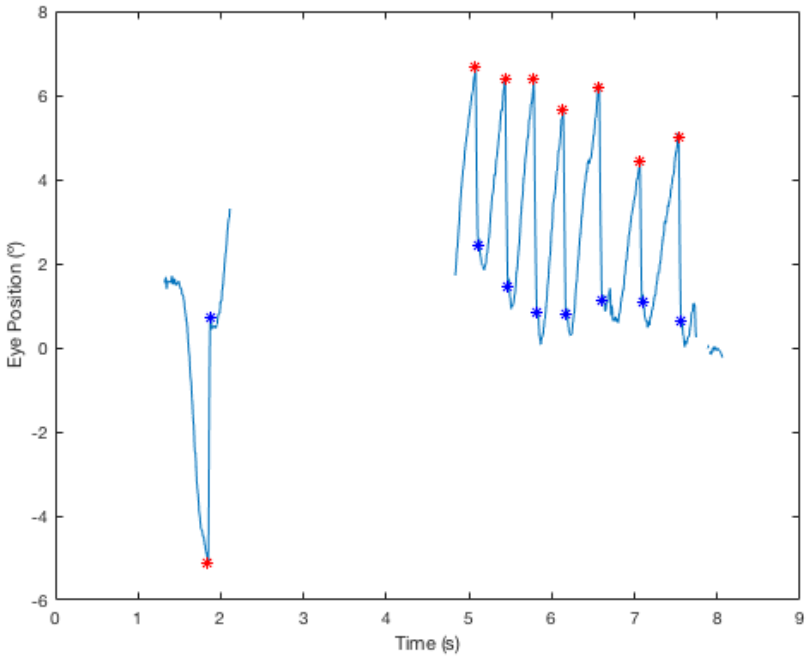


Figure 5.20 Saccades (fast phases) selected from the eye movement data during fixation at the center of the screen, extracted from the SP task calibrated retrospectively. Red asterisk depicts beginning of saccade and blue asterisk depicts end of saccade

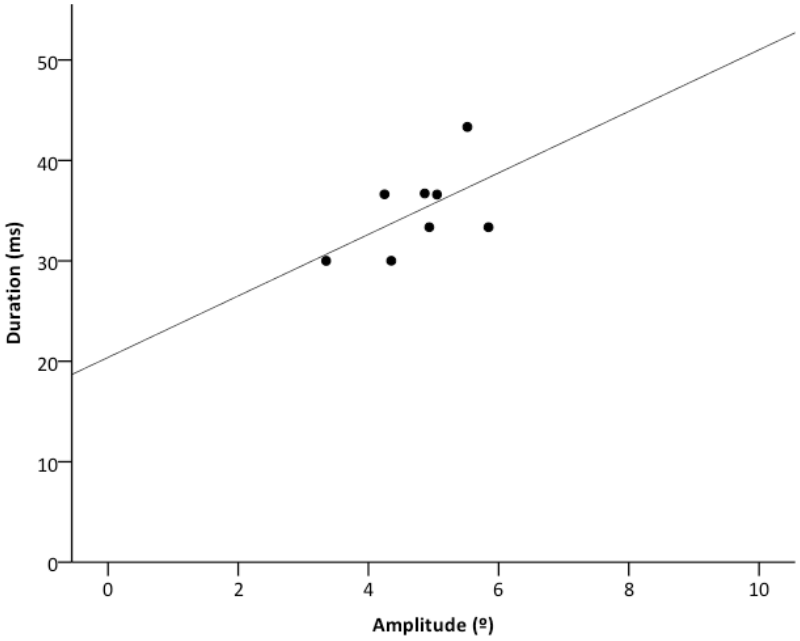


Figure 5.21 Amplitude-duration saccadic main sequence of saccades selected from the fast phases of the nystagmus waveform in Figure 5.20. The slope (3.06 ms/º) and intercept (20.39ms) value of the fitted line falls within the range of slopes and intercept values of published data (Garbutt, Harwood and Harris 2001)

5.8 Summary

Calibration of EMR data using smooth pursuit eye movements has been used in many nystagmus studies (Abadi and Scallan 2000; Clement et al. 2002; Jones 2011). However, there was no evidence of this method calibrating EMR data being validated or compared between nystagmus and non-nystagmus data in those studies. In the present study, I have shown that calibrating EMR data retrospectively can be applied to both nystagmus and non-nystagmus data using smooth pursuit eye movement data. I have also shown that retrospective calibration provides reliable results by demonstrating that the main sequence of the nystagmus fast phases follows the typical saccadic main sequence; this has not been previously reported.

The smooth pursuit method uses the entire waveform and hence many data points, compared to using the saccades which would result in a single datum per saccade (i.e. one datum of saccade amplitude plotted against duration). It also does not require segmenting out slow phases from fast phases, and therefore there is no need to consider the accuracy of segmentation, which may not work for all known waveforms of IN.

Ideally, data from vertical pursuit should be used to calibrate vertical eye position data. To shorten the duration of the EMR procedure, I did not ask the children in this study to perform vertical pursuit task, so vertical pursuit data were not available. Nonetheless, I have shown that using the slope and intercept values obtained from the horizontal pursuit data is sufficient to calibrate vertical eye position data.

Calibrating the EMR data retrospectively is a more practical approach when involving children. Pre-calibration of the eye tracker system would require an acceptable calibration before being able to proceed with the EMR. This would mean repeating the pre-calibration procedure to obtain an acceptable calibration. As children have short attention span,

repeating the same task multiple times could cause them to lose interest in the whole EMR procedure.

Typically, calibration of EMR data using fixation data at a number of known target positions on the screen would be ideal. However, fixations at different gaze positions was not the aim of this study. In addition to that, very young children will not understand the instruction to serially fixate at each target position. Following a single target is more within their capabilities, and if interesting, is almost reflexive (Hofsten and Rosander 1997; Grönqvist, Brodd and Rosander 2011; Pieh, Proudlock and Gottlob 2012). Therefore, I did not design a task that required the participant to fixate at different positions on the screen, which could have been used to calibrate the EMR data. In this chapter, I have shown that this method of retrospective calibration using pursuit data is reliable method for calibrating EMR data of nystagmus.

CHAPTER 6 CHARACTERISTICS OF NYSTAGMUS WAVEFORM IN CHILDREN WITH AND WITHOUT DOWN'S SYNDROME

6.1 Introduction

It is known that the nystagmus waveforms in both INS and FMNS are variable between individuals (Dell'Osso and Daroff 1975; Abadi and Bjerre 2002; Abadi and Scallan 2000). This can be demonstrated by the variability of foveation duration between individuals with INS, as illustrated in Figure 6.1 (Bedell 2000). According to Harris et al. (2012), there are two approaches to classifying the nystagmus waveform in INS: the "medical approach" and the "adaptationist approach". The first approach classifies the nystagmus waveform into 12 distinct types based on their shape and underlying motor mechanism (Dell'Osso and Daroff 1975; Dell'Osso 2012). The 12 waveforms will be described further in following sections. The second approach classifies the nystagmus waveform into two classes type 1 and type 2. The two classes are determined by examining the velocity profile of the nystagmus waveform. Type 1 nystagmus is associated with underlying velocity drive with normal downstream control, whereas type 2 waveforms are associated with either anomalous neural integrator or saccadic system with no oscillatory drive. The method of characterising nystagmus waveforms using this approach will also be discussed further in the following section.

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Figure 6.1 Variability of foveation duration between individuals with infantile nystagmus shown by Bedell (2000) indicating variability of the nystagmus waveform. Solid line illustrates mean visual acuity and shaded area illustrate 95% CI. Dashed line denotes normal visual acuity from Currie et al. (1993) and Chung and Bedell (1995)

The nystagmus waveforms in typically developing children have previously been characterised using the first approach (Abadi and Bjerre 2002; Theodorou et al. 2015). Characterising the specific type of nystagmus in children may give insight into the mechanism

behind this abnormal eye movement. There are no studies to date comparing the specific type of the nystagmus waveform between children with DS and typically developing children, although previous studies have characterised the nystagmus waveform in children with DS as general jerk or pendular for INS type of nystagmus (Averbuch-Heller et al. 1999; Felius, Beauchamp and Stager 2014; Weiss, Kelly and Phillips 2016). A more recent retrospective study by Oladiwura, Shweikh and Theodorou (2018) reported in general that 83.33% of the children with DS with nystagmus in their cohort were diagnosed with 'manifest horizontal nystagmus' which they presumed were all INS. The remaining 16.67% of children with DS in their study were reported to present with FMNS (6.25%), INS (8.33%) and internuclear ophthalmoplegia (2.08%).

We have established in Chapter 2 that children with Down's syndrome and nystagmus (DSN) have poorer acuity compared to typical children with nystagmus and children with DS who do not have nystagmus. Deficits in visual acuity of children with nystagmus (with and without DS) have been related to foveation using the Nystagmus Optimum Foveation Function (NOFF) (Felius et al. 2011; Felius, Beauchamp and Stager 2014). This method takes into account head and body movement, which is often the cause of noisy data that is very commonly seen in EMR data of children with nystagmus. The NOFF algorithm (see section 6.2.1) uses the horizontal eye velocity of <6º/s within ±0.5º as the foveation criterion, which is looked for in the EMR data in segments of 4 seconds (Figure 6.2). The advantage of NOFF is that it enables the quantification of nystagmus in noisy EMR data, which is often seen in children, as shown in Figure 6.3. Children with lower NOFF values (indicating a lower number of foveations in the nystagmus waveform) always have poorer acuity.

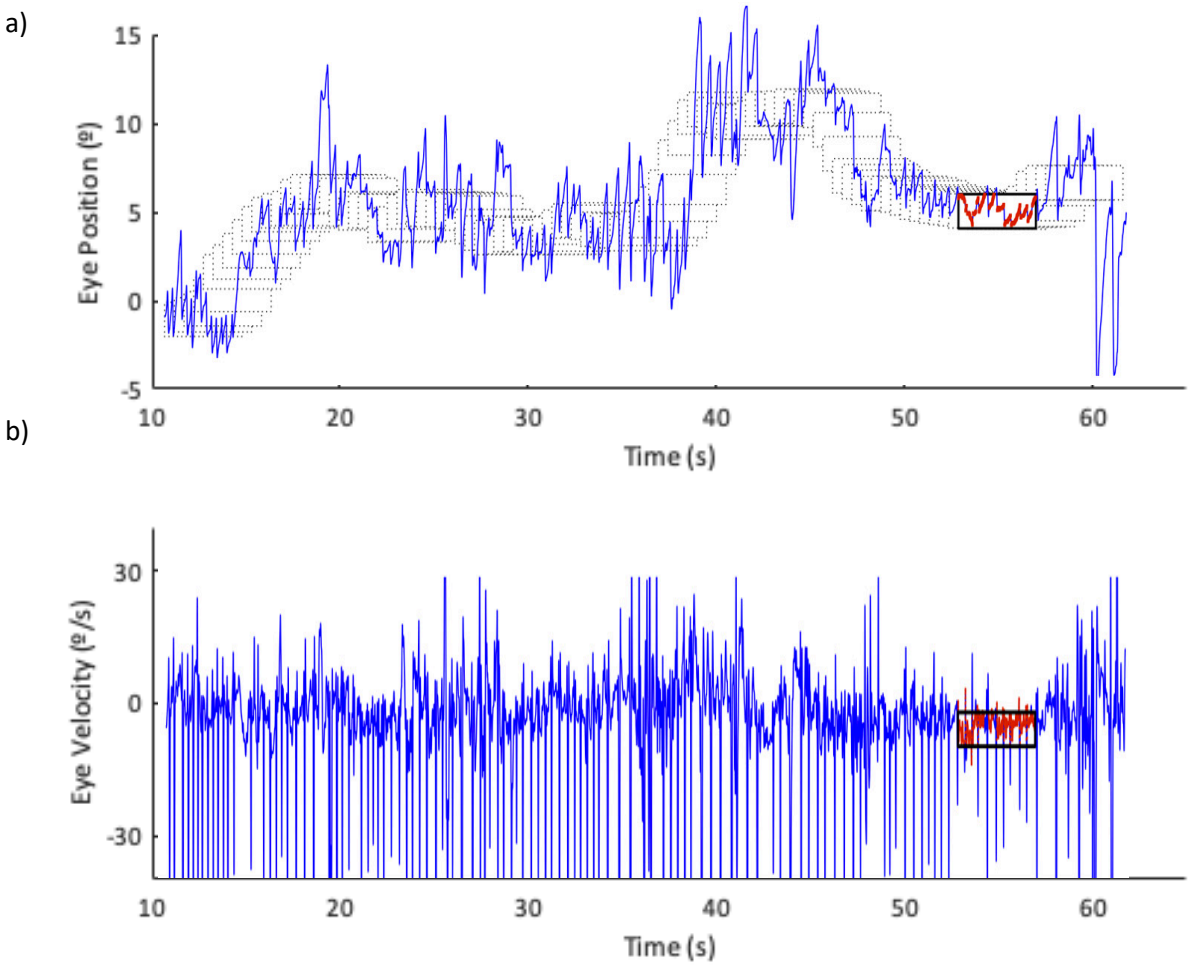

Figure 6.2 Illustration adapted from Felius et al. (2011) demonstrating how foveations are selected using the NOFF algorithm. Grey dotted boxes in (a) represents 4 second windows used to scan for the cleanest eye movement data. Solid boxes and data marked in red represents the cleanest data that fit the foveation criteria

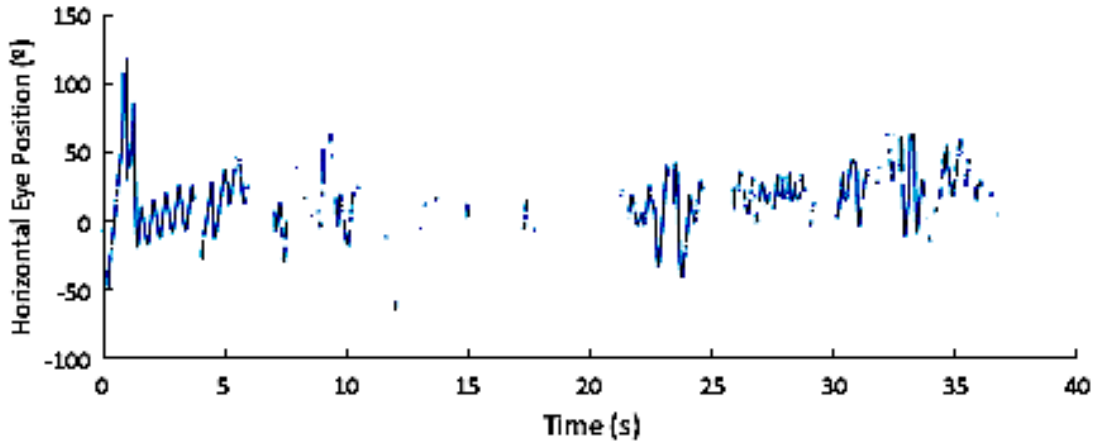

Figure 6.3 Example of an eye trace of a child with DS and nystagmus from the current study demonstrating noisy eye movement data that are encountered in this study, similar to that shown in Figure 6.2

The objective of this study was to compare the nystagmus waveform types between children with and without DS on both horizontal and vertical axes by classifying INS and FMNS waveform types using both the medical and adaptationist approach. I also look at the accuracy and precision during fixation in children with nystagmus with and without DS compared to children without nystagmus, using two-dimensional analysis of the nystagmus waveform components and their relationship to visual acuity and NOFF values.

6.2 Analysis of nystagmus waveform

EMR data were extracted from the Tobii Studio, processed using MATLAB as described in section 3.5, and then calibrated as explained in Chapter 4. To characterise the nystagmus waveform, data of either the fixation task or the smooth pursuit task were used. Smooth pursuit (SP) data were only used if the fixation data was unusable due to a lot of noise or too many missing data. In these cases, eye positions when the participant was fixating at the centre of the screen before the SP task started was extracted and used for analysis (Figure 6.4). If these data could not be used, then fixation data at either +10º or -10º between each

SP ramp were used (Figure 6.5). Otherwise, the data of eye positions (EP) when the eyes were pursuing the target were used.

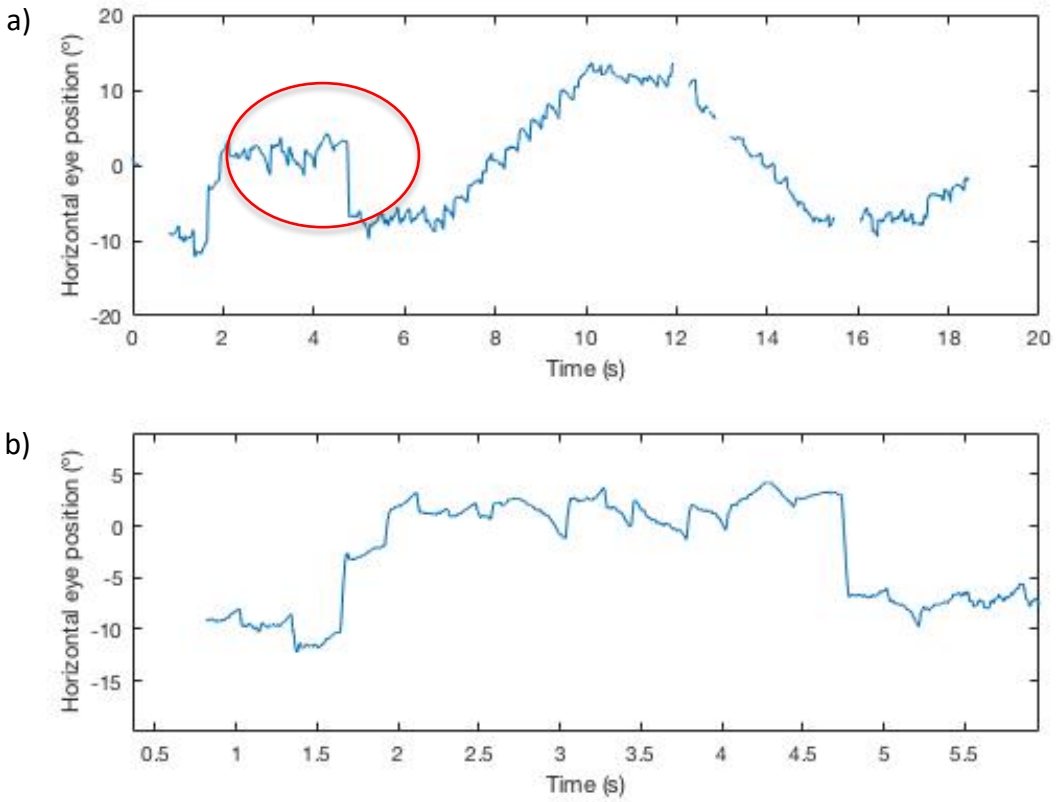

Figure 6.4 a) Eye trace of smooth pursuit task (SP) performed by participant P31. b) Magnification of highlighted data in (a) during fixation at center of the screen before the SP task started, used to characterize the nystagmus waveform

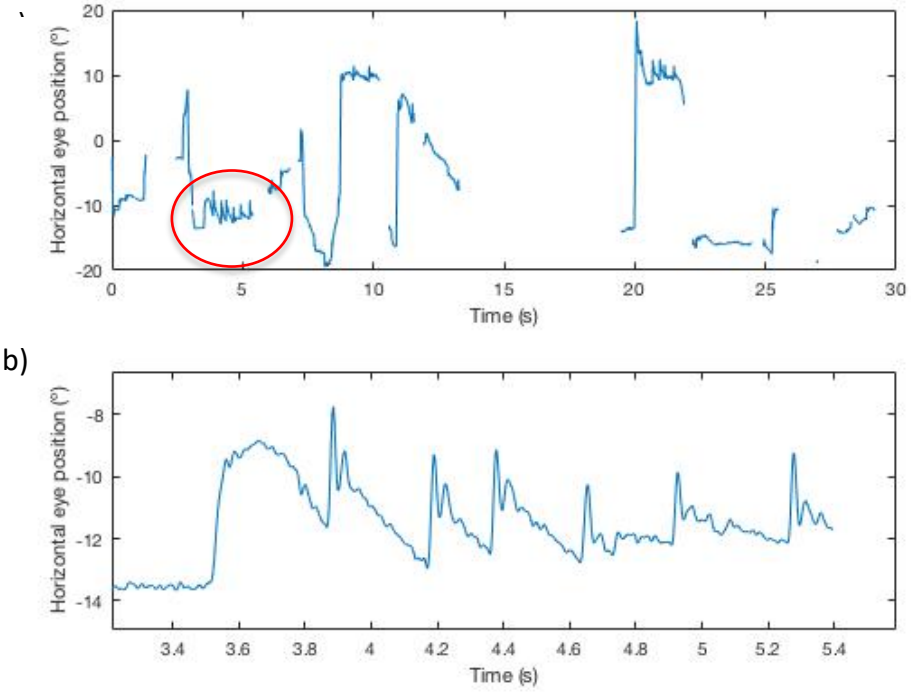

Figure 6.5a) Eye trace of smooth pursuit task (SP) performed by participant P72. b) Magnification of the data while the participant was fixating while the target was at -10º (red circle) that was used to characterize the nystagmus waveform

6.2.1 Quantifying the nystagmus waveform

The fast phases of the nystagmus waveform have been shown to have the same characteristics as saccades (Ron, Robinson and Skavenski 1972; Harrison et al. 2015). In order to determine the metrics of the nystagmus waveform, the saccades (i.e fast phases) need to be detected beforehand using the algorithm described in Chapter 3, section 3.6. Once the saccades were detected, the algorithm produced an output of the eye position data superimposed on the detected saccades (Figure 6.6). The output was inspected to ensure saccades were detected correctly. Once the detected saccades were accepted, the algorithm produced the following output for each saccade and slow phase:

- Duration
- Mean velocity

- Amplitude
- Direction

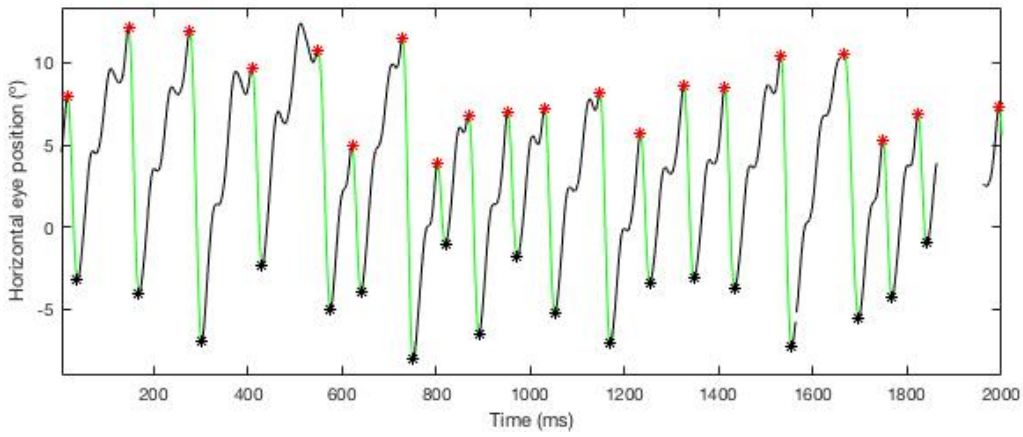

Figure 6.6 Eye trace of horizontal eye positions superimposed with detected saccades (marked in green) showing saccade onsets (red asterisks) and saccade offsets (black asterisks). Black line shows the slow phase component of the nystagmus waveform

All data that fall between the end of one saccade (saccade offset marked by black asterisk in Figure 6.6) and the beginning of the next saccade (saccade onset marked by red asterisks in Figure 6.6) were considered the slow phase of the nystagmus waveform. The amplitude of individual fast and slow phases was determined by calculating the difference between the absolute minimum and maximum eye position during each fast phase and slow phase. As the amplitudes of each slow phase were variable, the nystagmus amplitude was defined as mean of the slow phase amplitudes. The nystagmus intensity was derived on cycle-by-cycle basis, calculated by dividing the amplitude of each slow phase by its duration. Again, as the amplitude of each slow phase was variable, the nystagmus intensity was defined as the mean intensity of all the slow phases. This method of calculating intensity is mathematically similar to multiplying the nystagmus amplitude by its frequency.

Foveations and nystagmus optimal foveation function (NOFF) were determined using automated software in MATLAB generously provided by Dr Matt Dunn. The software uses an algorithm that searches for foveations in complete nystagmus cycles only, by calculating the total duration of the slow phases in each cycle and then searches for the slowest periods of the eye movements (i.e. 'lowest mean velocities') that continues for 10% of the slow phase duration (Dunn et al. 2018). NOFF, as described in Chapter 1, was calculated based on the algorithm designed by Felius et al. (2011) using the following formula:

$$NOFF = \log\left(\frac{foveation\ fraction}{1 - foveation\ fraction}\right)$$

Foveation fraction was defined as the percentage of data in the 4 seconds segment of clean fixation in a recording that satisfies the foveation criteria (horizontal eye velocity of <6º/s within ±0.5º). The NOFF values were described in logit units.

6.2.2 Classification of the nystagmus waveform

Early onset nystagmus can be divided into the 3 classes: INS, FMNS and SNS. The characteristics of each class have been described in Chapter 1. To determine whether the nystagmus waveform was INS or FMNS, the acceleration profile of each slow phase was determined. A 9-point moving average in each slow phase velocity was obtained with a built-in MATLAB function called 'movmean' to smooth out the noise in the data when calculating the acceleration. Figure 6.7 illustrates the data before and after being filtered using the 9-point moving average. The purpose of filtering the velocity data further was so that the trend of the acceleration data could be assessed without the interference of noise in the data.

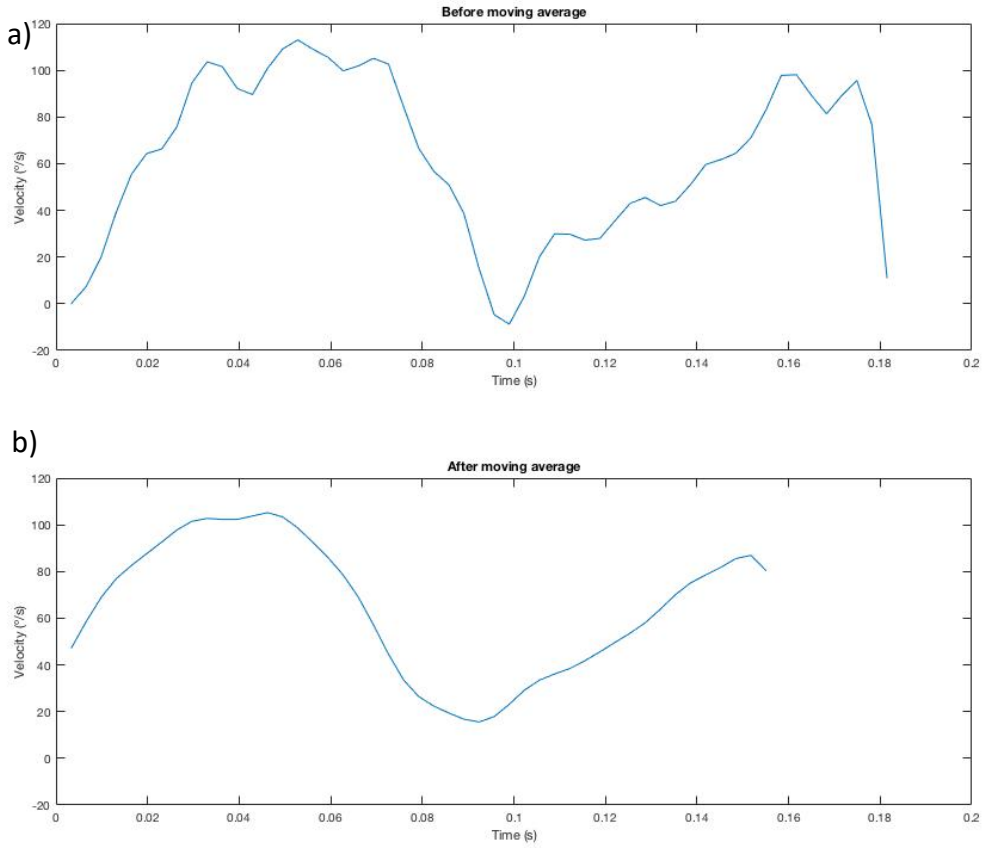

Figure 6.7 Plot of velocity against time before (a) and after (b) being smoothed using a 9-point moving average

The acceleration profile of each slow phase was then determined by looking at the change in the velocity data over time, obtained by differentiating the new velocity data. The value of the differentiated data was assigned as 1 for positive values, -1 for negative or 0. The percentage of these values was then calculated. If the percentage of 1 was more than 51%, the slow phase was determined to be increasing in acceleration. On the other hand, if the percentage of -1 was more than 51% then the slow phase was decreasing in acceleration. If the percentage of 0 was more than 51%, then it was deemed to be linear (i.e. constant velocity). The total number of slow phases with increasing, decreasing and constant velocity was then determined.

INS waveforms were characterised by accelerating slow phases, whereas FMNS waveforms were characterised by decelerating or linear slow phases, as recommended by the Classification of Eye Movement Abnormality and Strabismus (CEMAS) Working Group (Avallone et al. 2001). However, classification of FMNS type waveform would also require EMR while one eye is occluded to show the nystagmus beat direction is towards the fixating eye and also an increase in intensity during monocular occlusion (Hertle and Dell'Osso 2013). Since recording during monocular occlusion was either unsuccessful or not attempted in our group of participants due to lack of cooperation, waveforms with decelerating or linear velocity were all classified as FMNS-like.

6.2.2.1 Classification of INS waveforms

INS type waveforms were further classified using the "medical model", and the "adaptationist approach" as described by Harris et al. (2012). The medical model classifies the INS waveform into the 12 classes of oscillation as described by Dell'Osso and Daroff (1975). These different types of INS classes are pendular (P), asymmetric pendular (AP), pendular with foveating saccades (PFS), pure jerk (J), jerk with extended foveation (JEF), pseudo pendular (PP), pseudo pendular with foveating saccades (PPFS), pseudo cycloid (PC), pseudo jerk (PJ), triangular (T), dual jerk (DJ) and bidirectional jerk (BDJ) (see Figures 1.4 to 1.7 in Chapter 1). An example of a nystagmus waveform classified as JEF is illustrated in Figure 6.8.

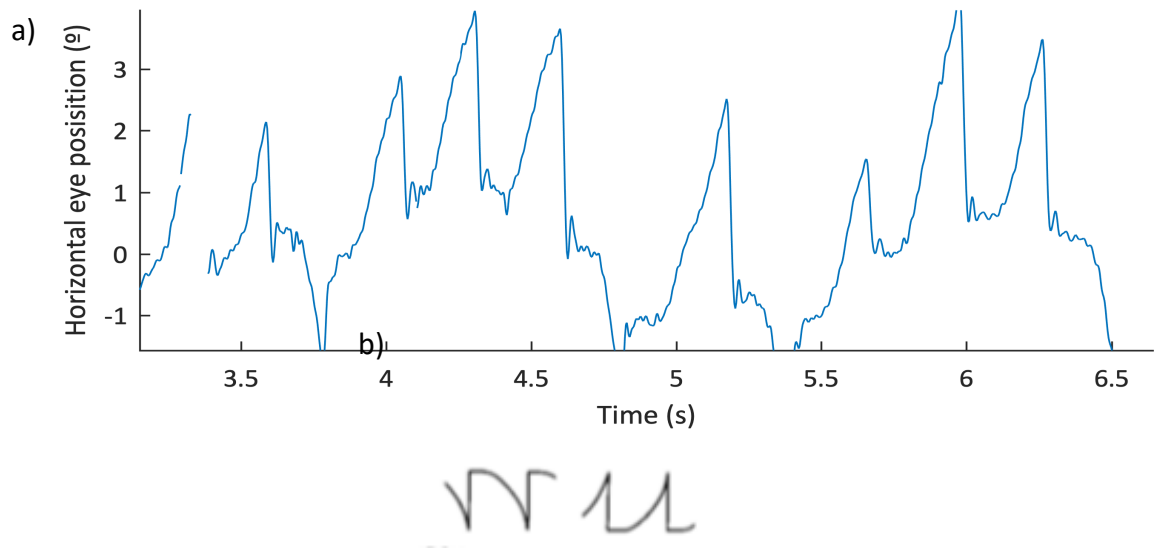

Figure 6.8 a) The nystagmus waveform of participant P59 classified as jerk with extended foveation (JEF). b) The classic JEF waveform as described by (Dell'Osso and Daroff 1975)

The adaptationist approach classifies the waveforms into two types, Type 1 and Type 2, based on the eye velocity (Harris, Waddington and Erichsen 2012). In Type 1 waveforms, the eye velocities after a fast phase were predicted to be unchanged, i.e. as if the fast phase did not occur (Figure 6.9a and 6.9b). Type 2 waveforms would have 'classic accelerating' slow phases, which then decrease in velocity. Moreover, eye velocities after the fast phase were noticeably different from the eye velocities before the slow phase occurred (Figure 6.9c). Using this method of classification, the waveforms of the children participating in this study were matched to the ones in

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Figure 6.10 and Figure 6.11

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Figure 6.9 Schematic example of Type 1 and Type 2 waveform as shown in Harris et al. (2012).

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Figure 6.10 Example of Type 1 velocity trace taken from Harris et al. (2012) to match with the waveforms of the children in the present study

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Figure 6.11 Examples of Type 2 waveforms taken from Harris et al. (2012) to match with the waveforms of the children in the present study

6.2.2.2 FMNS-like waveform

FMNS-like waveforms were further classified into the four types of MLN as described by Abadi and Scallan (2000). The four types of FMNS showed the following state under binocular viewing: stable (Type 1), square wave jerks (Type 2), torsional nystagmus (Type 3) and horizontal MLN (Type 4). A schematic illustration of these four types of MLN is illustrated in Figure 6.12.

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Figure 6.12 A schematic illustration of the for different types of MLN distinguished by the waveform pattern under binocular viewing as described by Abadi and Scallan (2000)

6.3 Results

6.3.1 Presentation and diagnosis of nystagmus

A total of 28 children with DSN (male, n=16; female, n=12) and 17 children with TN (male, n= 12; female, n= 5) participated in this study. The age range of the children in the DSN group was between 2.16 – 17.51 years (mean 6.13 $\pm$ 4.07SD years) and TN group was between 0.64

and 12.99 years (mean 5.20 ± 4.06SD years). Parents of 20 children were able to provide reliable information on the onset of nystagmus (i.e. when they first noticed the nystagmus present). Seven children with DSN and 7 children in the TN group presented when they were less than 6 months old. Nystagmus was noticed at birth in two of these children (1 DSN and 1 TN). Five parents noticed the nystagmus between 6 and 12 months (4 DSN and 1 TN). Parents of only one child (DSN) noticed the presence of nystagmus at 4 years of age.

Twenty-one parents provided the name and address of the participant's ophthalmologist. Parents of two children in the DSN group (P69 and P82) provided a report from their child's ophthalmologist. One child in the TN group (P83, 7.66 months old) was scheduled for further assessment at the hospital and awaiting diagnosis at the time of the study visit. Letters were sent to the ophthalmologists of 18 children in the DSN group and 3 children in the TN group. Twelve responses with the details of the participant's diagnosis were received. One ophthalmologist responded that the named child was not seen in their clinic. Therefore, information on the diagnosis of nystagmus was available for 14 children (11 DSN and 3 TN) including the 2 children with DSN whose parents provided the reports from their ophthalmologist.

A summary of the diagnosis of nystagmus is tabulated in Table 6.1. The age of diagnosis of children in the DSN group ranged from 8 to 31 months. Two children in the TN group were diagnosed at 10 and 11 months. One child had a gradual diagnosis, which was finalised at the age of 7 years old. Four parents of children with TN provided information on the age at diagnosis, where the range was between 4 and 12 months.

Diagnosis	DSN (n=11)	TN (n=3)
INS	4	3
Pendular	1	-
Horizontal nystagmus	1	-
LN / FMNS	2	-
Unknown	2	-
No nystagmus	1 (P37)	-

Table 6.1 Diagnosis of nystagmus for 11 children with DS and nystagmus (DSN) and typically developing children with nystagmus (n=3)

Five children with DSN were diagnosed with INS. For these 5 children, the ophthalmologist simply wrote 'Down's syndrome' as the associated condition. Of these 5 children, 2 had other associated symptoms such as anisometropia (P34), alternating esotropia (P34), and myopia (P69). One child in the DSN group was associated with high myopia (P46) and another was associated with hypermetropic astigmatism (P75). None of the 3 children in the TN group had any associated conditions.

Table 6.2 summarises the methods performed to investigate nystagmus as reported by the ophthalmologists. Four of the children in the DSN group had orthoptic assessment only. Only one child (P68) had ERG, VEP and orthoptic assessment and another child had an MRI scan. Another child in the DSN group whose parents provided the ophthalmologist report (P69) had a full eye examination under general anaesthesia. However, the investigation of nystagmus was not stated. Two children did not have any investigation done. All three children in the TN group had ERG, VEP, and orthoptic assessment performed.

Method of investigation	DSN (n=11)	TN (n=3)
VEP	1(P68)	3 (P71, P74, P80)
ERG	1(P68)	3(P71, P74, P80)
EMR	-	-
OA	6(P34, P62, P67, P68, P75)	3(P71, P74, P80)
MRI	1(P46)	-
Others	1(P69)	-
No investigation	1(P82)	-

Table 6.2 Methods performed to investigate nystagmus as reported by ophthalmologists. (VEP = Visual evoked potential; ERG = Electroretinogram; EMR = Eye movement recording; OA = Orthoptic assessment; MRI =Magnetic resonance imaging)

6.3.2 Visual Acuity

Figure 6.13 illustrates the distribution of binocular visual acuity (BVA) successfully measured in 26 children in the DSN group (mean = 0.63 $\pm$ 0.34SD logMAR) and 14 children in the TN group (mean = 0.54 $\pm$ 0.35SD logMAR). Both groups of children showed a normal distribution of BVA (DSN, p=0.09; TN, p=0.52) when tested with the Shapiro-Wilk test of normality. Monocular VA was only available for 3 children in the DSN group and 8 children in the TN group, as shown in Table 6.3. An independent sample t-test was employed to compare the BVA between children in the DSN and TN group. Results show no significant difference in BVA between the two groups of children ($t(14) = 0.92$, $p=0.37$).

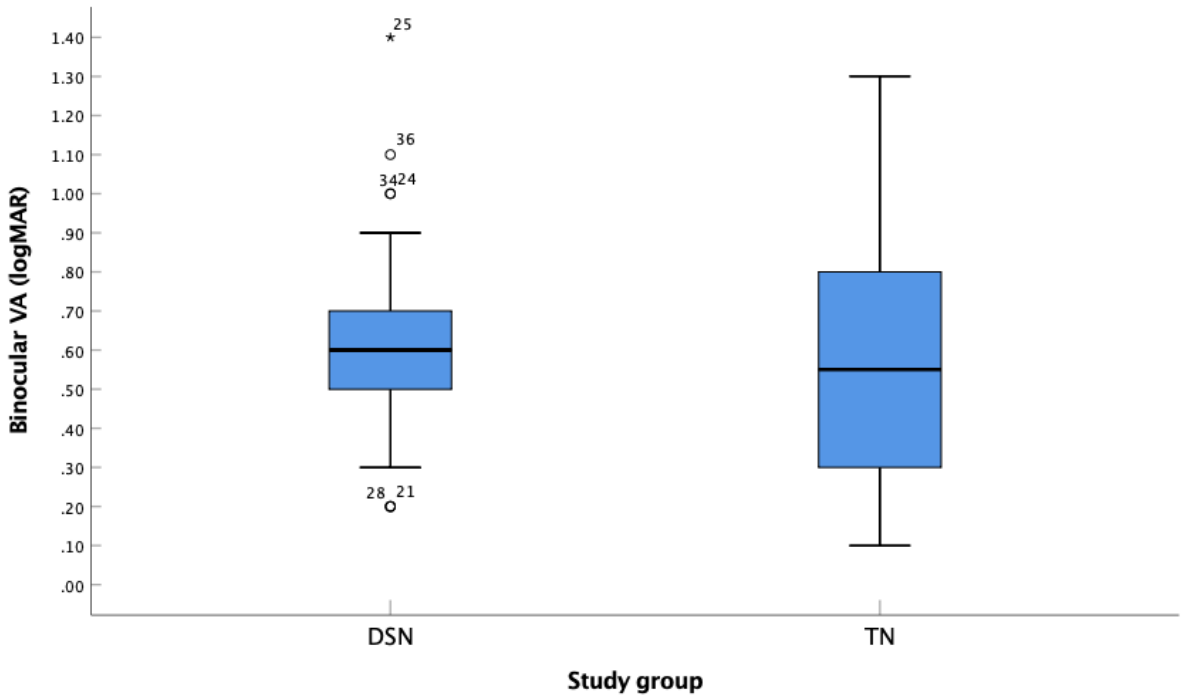

Figure 6.13 Distribution of BVA of children in the DSN and TN group

Participant	Group	Age (years)	VA RE (logMAR)	VA LE (logMAR)
P05	DSN	14.9	0.75	0.9
P15	DSN	17.5	0.8	0.9
P37	DSN	5.26	0.6	0.6
P04	TN	12.9	0.2	0.3
P32	TN	3.2	0.5	0.8
P57	TN	7.6	0.1	0.3
P58	TN	17.8	0.8	0.3
P59	TN	4.3	0.4	0.4
P60	TN	7.2	0.3	0.4
P71	TN	6.2	0.1	0.3
P80	TN	11.1	0.5	0.7

Table 6.3 Monocular visual acuity of children in the DSN and TN group

6.3.3 Refractive error

Refractive error was successfully measured in 39 of the children (26 DSN and 13 TN). The same refractive error criteria described in Chapter 2, section 2.3.6 were applied. Ten children in the DSN group and 7 in the TN group were anisometropic, including the child with DSN reported by the ophthalmologist. In these children, the eye that was the least ametropic was chosen to be analysed. In all other cases, the right eye was used for analysis of the refractive error. Seventeen (65.4%) children in the DSN group and 10 (76.9%) children in the TN group presented with significant refractive error. The most frequent type of refractive error in both groups of children was hyperopia (DSN 52% and TN 75%). Sixteen (65.4%) children in the DSN and 4 (30.7%) children in TN group presented with significant astigmatism. The most common type of astigmatism in DSN group and TN group was WTR. Results of Fisher's exact test showed no significant association between children with nystagmus, with and without DS, and the type of refractive error (p=1.00).

6.3.4 Strabismus

The Hirschberg and cover test showed that 8 (28.57%) of the children in the DSN group presented with esotropia (SOT), which was the only type of strabismus seen in this group of children. Four of these children presented with nystagmus when one eye was covered (a characteristic of FMNS). Three children in the TN group presented with SOT and 1 presented with exotropia.

6.3.5 Null point

Thirty-eight (22 DSN and 16 TN) of the children presented with oscillation of the eyes under binocular viewing during optometric assessment suggesting INS. Six children in the DSN group only exhibited oscillation when one eye was covered, suggesting FMNS. However, it was difficult to determine the direction of the nystagmus beat under the occlusion of each as

trying to maintain the eye occluded for even a short period of time proved challenging in these groups of children. Oscillation of the eye was not seen in one child with DSN (P72) under either binocular or monocular viewing during the optometric assessment, but EMR showed presence of low amplitude (2º), low frequency (0.5Hz) waveform with decelerating slow phases, consistent with FMNS. Null position was defined as the gaze angle where the oscillation of the eye was at a minimum (Abadi and Bjerre 2002). Obvious null position was observed in 22 of the 38 children that presented with nystagmus under binocular viewing (see Table 6.4 and Table 6.5). The relationship between the presence of a null position and age for each group of children was determined using the Spearman's rho test. No significant correlation was seen between age and the observation of null position in both children with DSN ($r(8) = 0.28$, $p = 0.49$, $R^2 = 0.08$) and children in the TN group ($r(8) = 0.12$, $p = 0.77$, $R^2 = 0.01$).

6.3.6 Nystagmus waveform characteristics

EMR was performed on all 45 children with nystagmus but was only successful in 21 (48.88%) children (11 DSN, 10 TN). EMR of both the fixation and SP tasks was successful in 12 children (6 DSN, 6 TN). Two children in the DSN group only had successful recording for the fixation task. Therefore, only a subjective classification of the nystagmus waveform type could be performed on the data for these two children, as the fixation data could not be calibrated without SP data. The remaining 9 children (5 DSN, 4TN) had successful recordings for SP task only. However, data of one child in the DSN group (P69) could not be used to quantify the nystagmus waveform or eye movement performance because the child did not follow the stimulus during the pursuit task. Therefore, the data of that particular child was only used for the classification of nystagmus type.

6.3.6.1 Nystagmus plane

Oscillation of the eyes can be horizontal, vertical or torsional. Since the eye tracker used in this study was a video-based type, it was only possible to analyse the nystagmus motion in the horizontal and vertical axis. No children presented with oscillation in the vertical axis only. Thirteen children (DSN = 9; TN = 4) exhibited oscillation in the horizontal axis only and 6 children (DSN = 1; TN = 5) exhibited oscillation in both the horizontal and vertical axis. I was unable to determine the type of oscillation in one child in the TN group. The eye trace for each child can be found in Appendices I and J.

6.3.6.2 Nystagmus type

Slow phases of 9 (40.9%) children in the DSN and all 11 (100%) children in the TN group showed an accelerating profile, suggesting INS. Three children in the DSN group (P34, P72 and P82) showed a nystagmus waveform that was FMNS-like (i.e. decelerating or linear slow phases). One child in the TN group (P04) did not show any nystagmus waveform when fixating at the centre of the screen but showed a jerk waveform when fixating at a target placed at -10º (Figure 6.14).

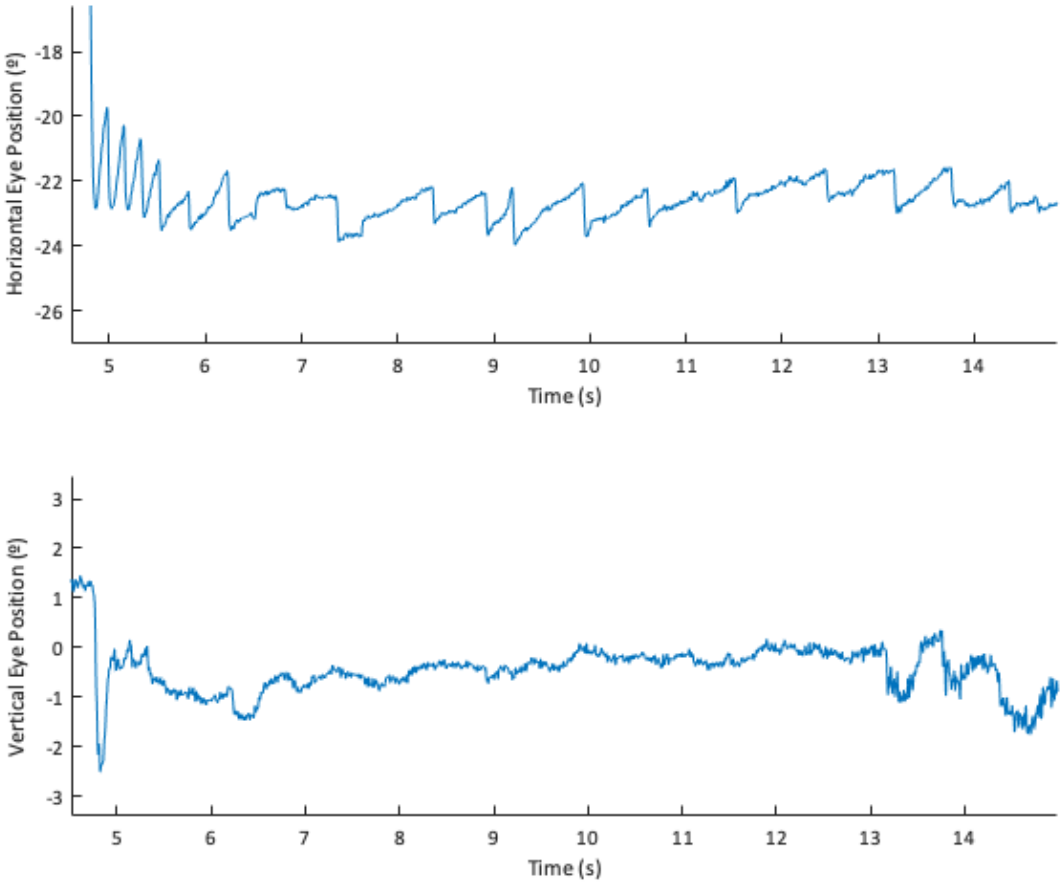

Figure 6.14 Horizontal and vertical eye trace of participant P04 showing jerk waveform when viewing a target at -10º on the screen

The nystagmus waveform of the 20 children presenting with INS waveform were further classified into the 12 classical types (see Table 6.4 and Table 6.5). The most common type of oscillation observed in the DSN group was JEF (n=4), followed by PFS (n=3). Whereas in the TN group of children, the most common type of oscillation encountered was PFS (n=4) followed by PJ (n=3). Six children (4 DSN and 2 TN) presented with a combination of two INS waveform types. Younger children (between 1.16 and 3.33 years, n=5) in the TN group seem to present with the pendular type of nystagmus (both P and PFS). The older children in the TN group presented with the jerk type of nystagmus (either PJ, JEF, or PC). However, there

was no pattern seen in the nystagmus waveform type according to age in the DSN group. I was unable to establish the waveform type of two children (one in each group).

Two children in the DSN group (P72 and P82) exhibited FMNS-like waveform, with decreasing slow phases under binocular viewing, which is consistent with Type 4 MLN (Figure 6.15 and Figure 6.16). However, EMR under monocular viewing was unsuccessful, hence diagnosis of FMNS was impossible. Figure 6.17 shows the eye trace of participant P34 during binocular viewing. No ocular oscillation was observed. However, EMR recording showed nystagmus with a combination of decreasing and linear slow phases during occlusion (Figure 6.18 and Figure 6.19) when one eye was occluded. The nystagmus beat was towards the fixating eye. These characteristics are consistent with Type 1 MLN.

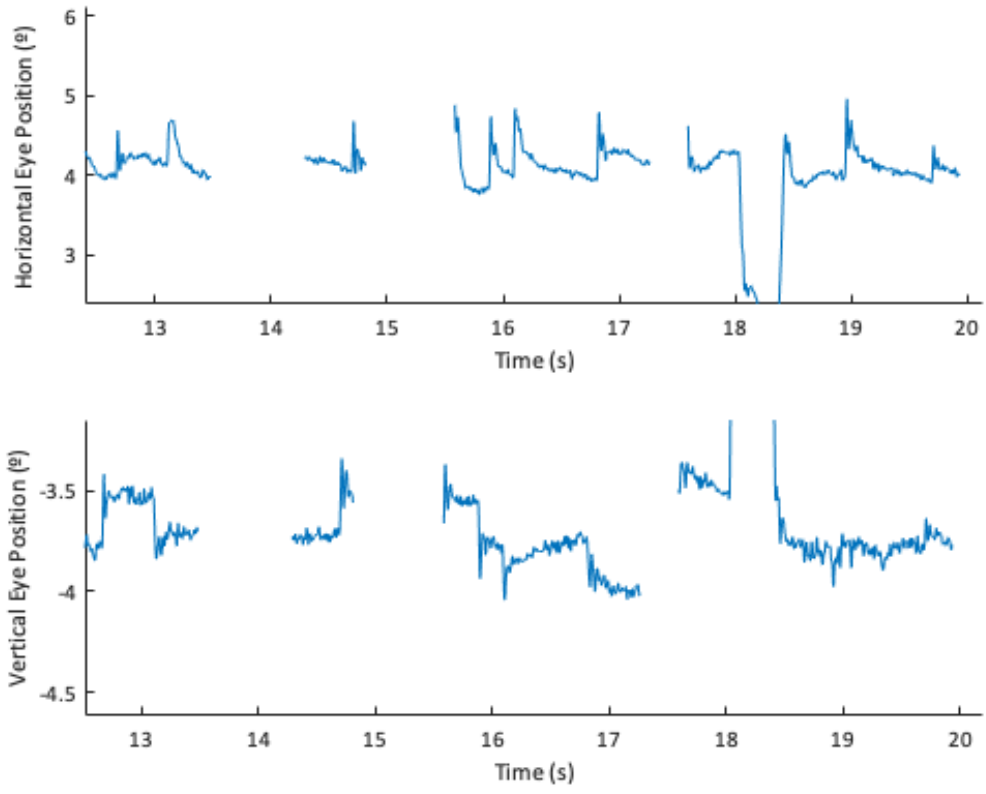

Figure 6.15 Horizontal and vertical eye trace of participant P72 showing nystagmus waveform with decreasing velocity in the right eye during binocular viewing

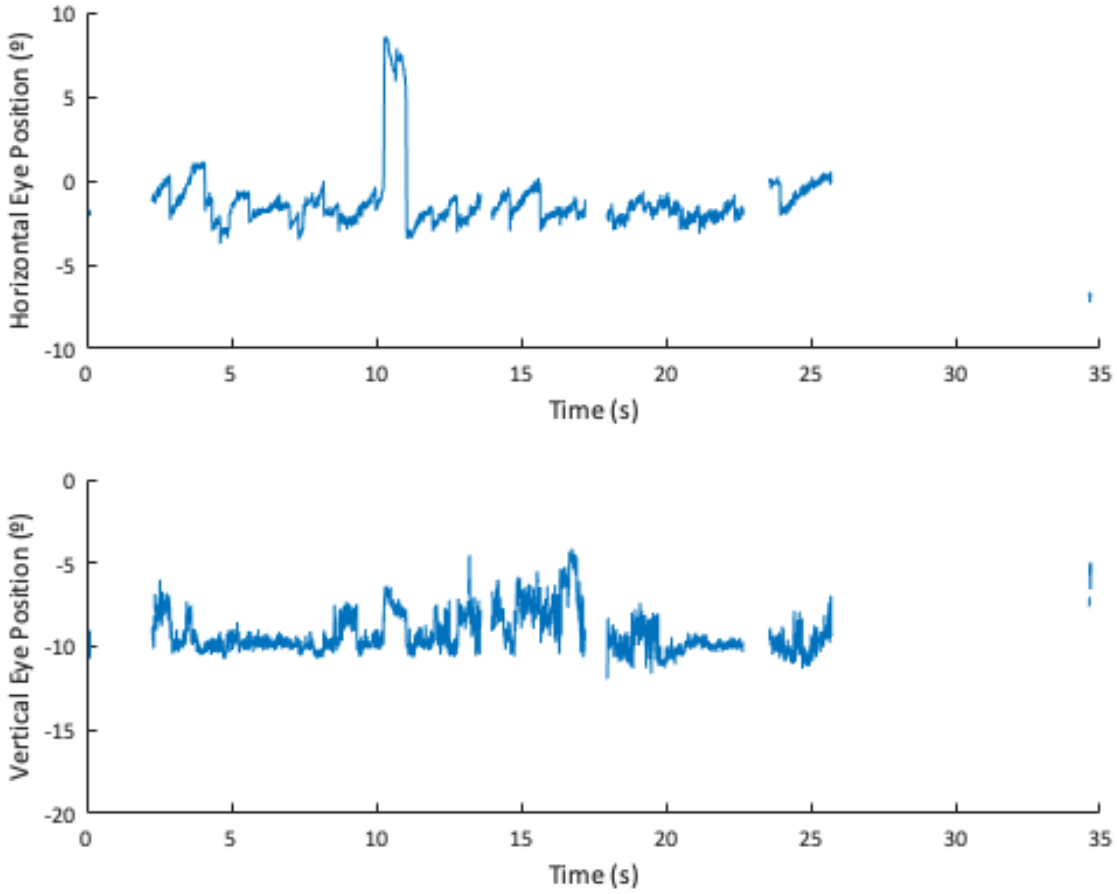

Figure 6.16 Horizontal and vertical eye trace of participant P82 showing nystagmus waveform with decreasing velocity in the right eye during binocular viewing

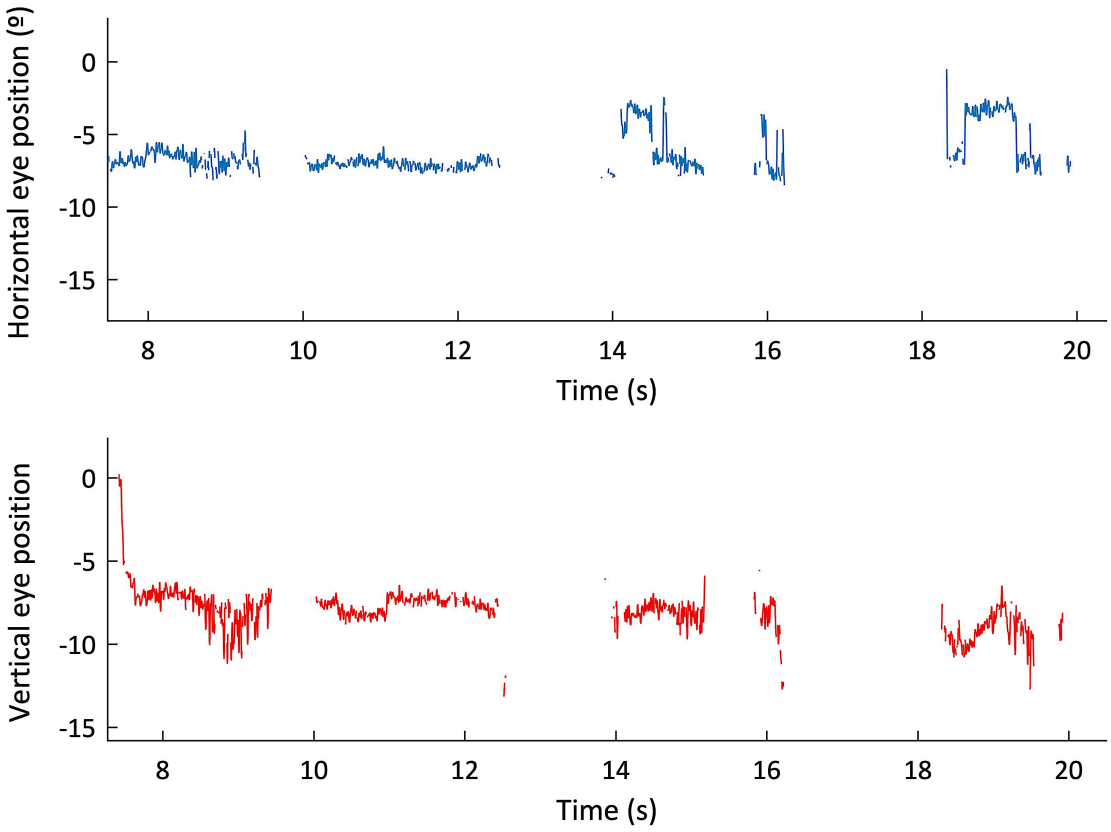

Figure 6.17 Horizontal and vertical eye trace of participant P34 showing no nystagmus waveform when viewing binocularly

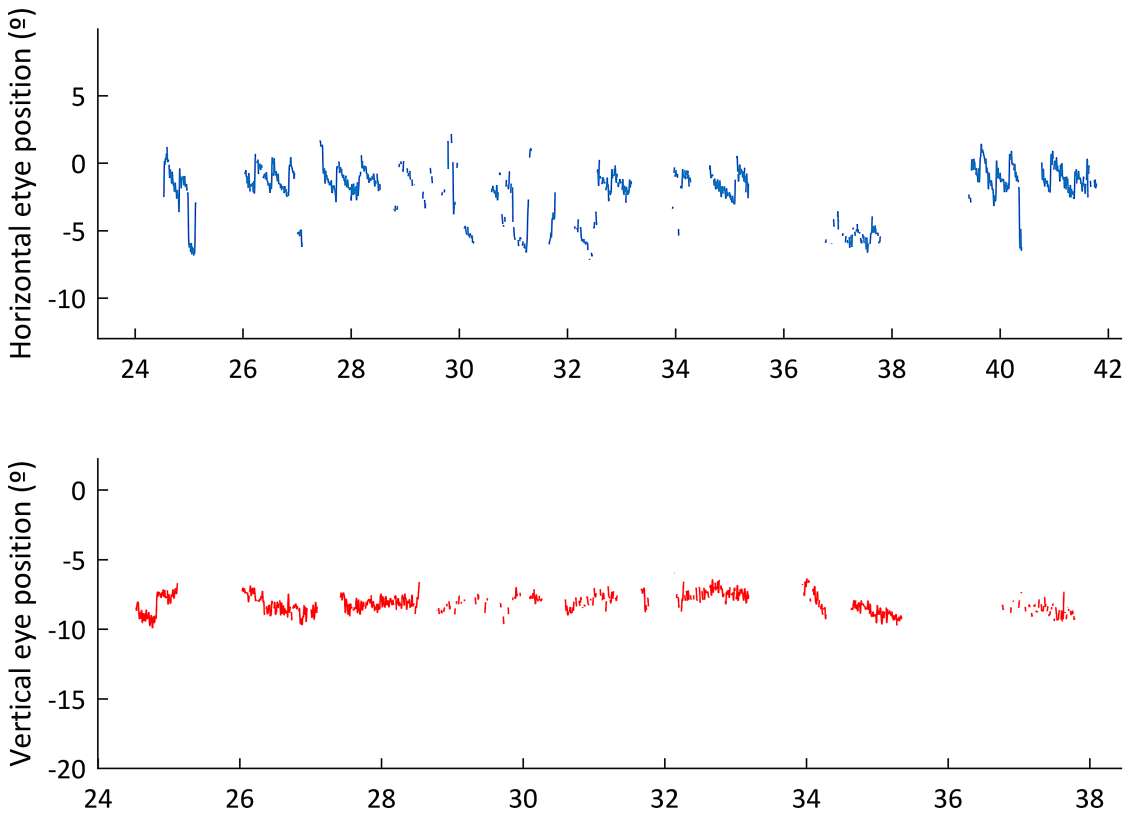

Figure 6.18 Eye trace of participant P34 showing right beating nystagmus waveform with decreasing and linear slow phases on the horizontal eye trace (a) when viewing with the right eye. No nystagmus waveform seen on the vertical axis (b)

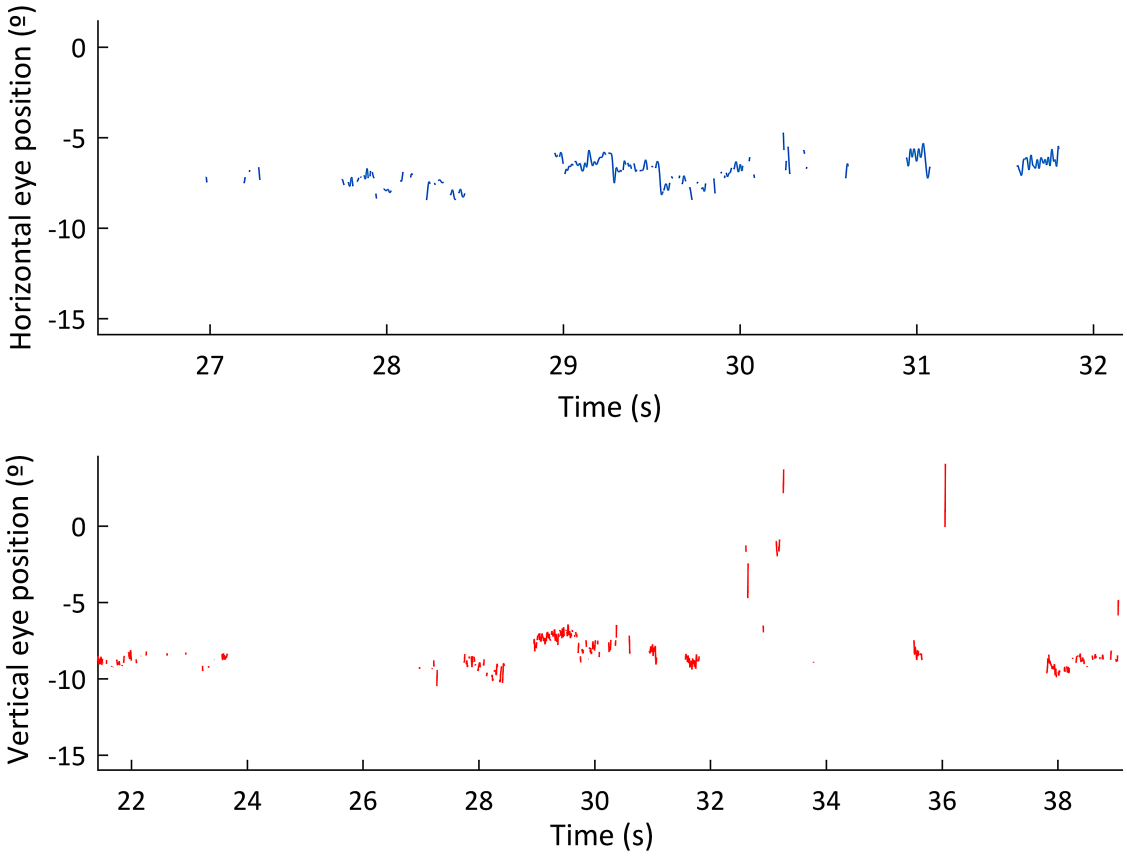

Figure 6.19 Eye trace of participant P34 showing left beating nystagmus waveform with decreasing slow phases on the horizontal eye trace (a) when viewing with the left eye. No nystagmus waveform seen on the vertical axis (b)

6.3.6.3 Nystagmus amplitude and intensity

Calibrated EMR data during fixation of 18 children (10 DSN and 8 TN) were analysed including the 3 children with FMNS-like waveform. The nystagmus amplitude of children in the DSN group ranged from 1.15º to 25.50º with a mean of 5.08º ± 7.38ºSD. Children in the TN group had amplitudes ranging from 0.24º to 15.70º with a mean of 6.95º ± 5.26ºSD (Figure 6.20). An independent t-test showed no significant difference in the mean amplitude between the two groups of children (t(16) = -0.61, p=0.55). The nystagmus intensity of children in the DSN group ranged from 2.63º/s to 63.70º/s with a mean of 14.53º/s ± 17.91º/s SD and children in the TN group had intensity ranging from 1.34º/s to 51.79º/s with a mean of 20.46º/s ±

51.01º/s SD (Figure 6.21). Similarly, there was no significant difference between the mean intensity in both groups of children (t(16) = -0.59, p=0.56).

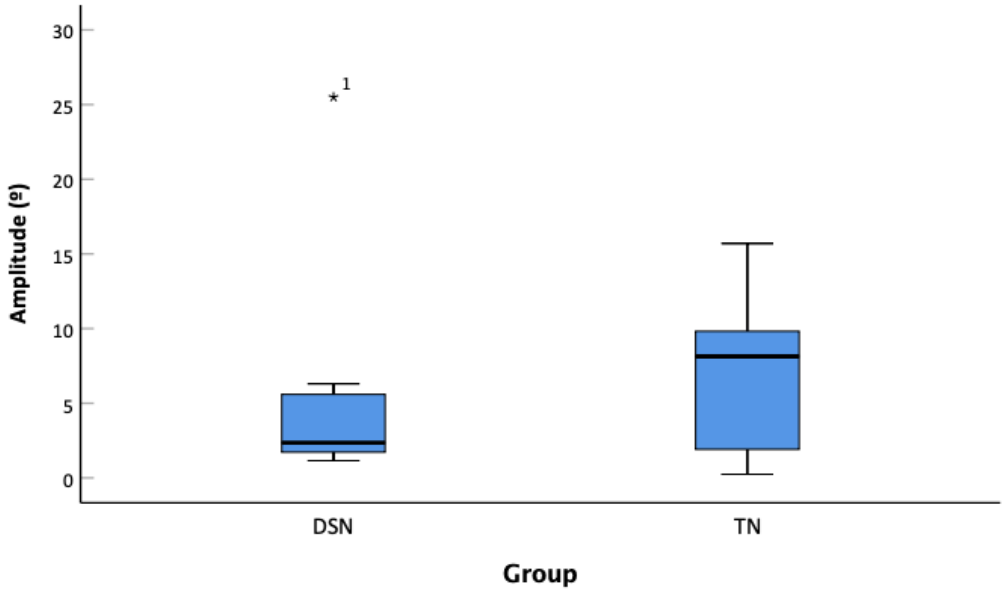

Figure 6.20 Mean nystagmus amplitude of children with DS and nystagmus (DSN) and typically developing children with nystagmus (TN). Error bars depict 95% confidence interval. Star indicates outlier

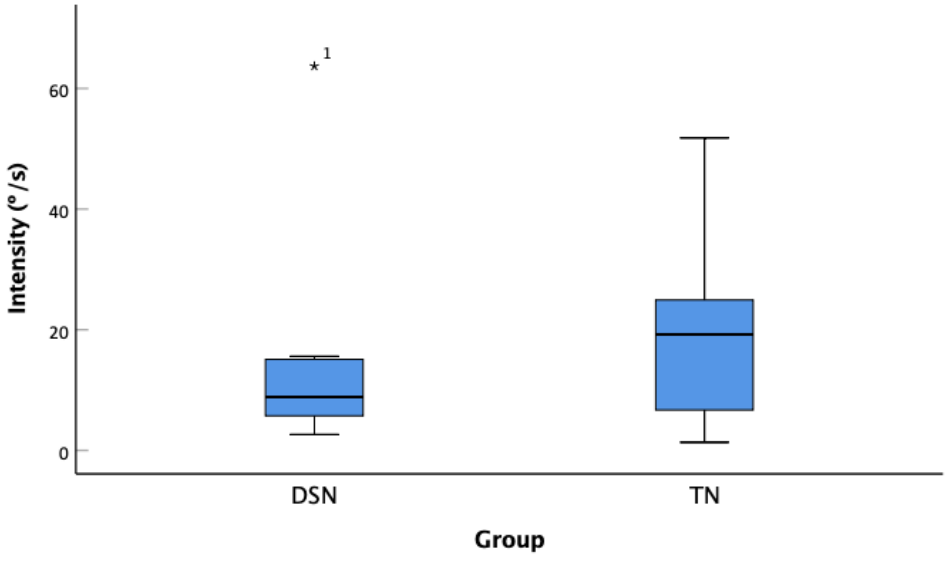

Figure 6.21 Mean nystagmus intensity of children with DS and nystagmus (DSN) and typically developing children with nystagmus (TN). Error bars depict 95% confidence interval. Star indicates outlier

6.3.6.4 Foveation and nystagmus optimal foveation function (NOFF)

Mean foveation duration was calculated for all participants exhibiting an INS waveform as other types of nystagmus (i.e. FMNS and acquired horizontal jerk nystagmus) do not have foveation periods (Dell'osso et al. 1992). The mean foveation duration of children in the DSN group ranged from 40.40ms to 52.90ms (mean 46.19ms ± 4.79SD). The mean foveation of children in the TN group ranged from 29ms to 65.60ms (mean 47.65ms ± 13.72SD). Results of independent t-test showed no significant difference between mean foveation of children in the DSN and TN group ($t(16) = -0.79$, $p=0.44$).

NOFF was calculated for all children in the DSN group and ranged from -4.51 logits to 1.62 logits (mean -1.62 logits ± 2.23SD) whereas children in the TN group had NOFF values ranging from -6.40 logits to 0.68 logits (mean -2.37 logits ± 2.73SD). One child in the DSN group (P15) had a NOFF value of infinity. This was because the nystagmus intensity of the participant P15 was high, producing a NOFF value out of the limit set by the algorithm, which was ±5 logits (Felius, Beauchamp and Stager 2014). When this occurs, the algorithm would output a NOFF value of "inf".

Code	Gender	Age (years)	Null (gaze position)	Task	Waveform type (EMR)		
					Horizontal Axis	Vertical Axis	Type
P15	M	17.51	Primary	SP	PFS	Nil	1
P17	M	2.76	Unable to determine	Fixation	DJ+PC	Nil	-
P22	M	3.31	Primary	SP	JEF + P	Nil	1
P31	F	11.50	Left	Fixation	JEF	Nil	1
P34	F	5.64	-	Fixation	Decreasing + linear slow phases under monocular viewing	Nil	FMNS-like
P36	F	9.12	-	SP	JEF + PJ	Nil	
P67	M	2.90	Primary + down	Ramp 2 SP at +10º Fixation	JEF	Nil	1
P69	M	6.80	Down left	SP	P + PFS	JEF	1
P72	M	4.71	-	SP	Decelerating slow phase	Nil	FMNS-like
P76	M	2.68	Primary	Fixation	PJ		-
P81	F	9.22	Primary	Fixation	PJ	Nil	Unable to determine
P82	M	1.19	Unable to determine	Fixation	Linear +decelerating slow phase	Nil	FMNS-like

Table 6.4 Summary of waveform type in children with DS and nystagmus (P= pendular, PFS = pendular with foveating saccades, P= pure jerk, JEF = jerk with extended foveation, PC = pseudo cycloid, DJ = dual jerk, BDJ = bidirectional jerk). SP = smooth pursuit

Code	Gender	Age (years)	EMR with RX?	Null (gaze position)	Task	Waveform type (EMR)		
						Horizontal Axis	Vertical Axis	Type
P04	M	12.99	N	Primary	Fixation	PJ	Nil	2
P14	M	3.33	N	Not obvious	Fixation	PFS	J	1
P32	M	3.20	N	-	SP	PJ + PFS	Nil	1
P53	M	10.36	N	Primary	Fixation	DJ	J+DJ+JEF	-
P57	F	10.96	Y	Left	Fixation	BDJ	Nil	1
P58	M	17.81	Y	Right	Fixation	Unable to determine	Unable to determine	1
P59	M	4.31	N	Primary	Fixation	JEF	Nil	2
P71	F	6.15	N	Primary	Fixation	PC + post saccadic oscillation	J	1
P74	M	2.41	N	Not obvious	SP	JEF + PFS	PC + P	1
P80	M	11.10	N	Down	Fixation	PJ	Nil	2
P83	F	1.16	N	Not obvious	SP	P+ PFS	J + DJ	2

Table 6.5 Summary of waveform type in typically developing children with nystagmus (P= pendular, PFS = pendular with foveating saccades, P= pure jerk, JEF = jerk with extended foveation, PC = pseudo cycloid, DJ = dual jerk, BDJ = bidirectional jerk). SP = smooth pursuit

Participant	Group	Task	Mean Amplitude (º)	Mean Intensity (º/s)	NOFF (logits)
P15	DSN	SP	26.35	102.95	-inf
P22	DSN	SP	1.13	10.14	-1.68
P31	DSN	Fix	1.48	6.13	-2.98
P36	DSN	SP RAMP 2	7.40	11.22	-1.66
P67	DSN	SP +10º	8.64	33.21	-4.51
P72	DSN	SP	3.80	10.34	1.05
P81	DSN	Fix	1.41	4.02	1.62
P82	DSN	Fix	1.35	2.63	
P04	TN	fix	1.70	9.38	0.24
P14	TN	Fix	3.02	12.82	-6.4
P53	TN	Fix	9.25	47.11	-2.67
P58	TN	Fix	8.73	41.85	-5.99
P59	TN	Fix	1.57	7.16	-1.84
P71	TN	Fix	9.76	30.22	-3.06
P74	TN	SP	47.61	202.49	0.07
P80	TN	Fix	1.02	2.30	0.21

Table 6.6 Summary of nystagmus waveform metrics of children with DSN and TN

6.4 Discussion

6.4.1 Presentation time/diagnosis of nystagmus

Infantile nystagmus has been reported to be present by the age of 6 months or earlier (Casteels et al. 1992; Avallone et al. 2001). This study found that the percentage of children with DSN (61.53%) detected with nystagmus before the age of 6 months was lower than children in the TN group (87.5%) in the present study and also typically developing children reported by (Abadi and Bjerre 2002). Nystagmus in infants can consist of amplitudes of approximately 3º (Theodorou et al. 2015), with frequencies of approximately 1 Hz and waveform types of asymmetrical pendular and pseudocycloid (Abadi and Dickinson 1986; Reinecke, Guo and Goldstein 1988; Theodorou et al. 2015). In cases of FMNS, the oscillations also have low amplitudes, or even no oscillation at all under binocular viewing. The oscillations become prominent when one eye is occluded (Abadi and Scallan 2000). Therefore, the abnormal eye movements may have been missed due to these conditions. Furthermore, some parents, especially the parents of firstborns, may not know that the ocular movements are abnormal, and therefore delay reporting the condition to their healthcare provider.

Based on the responses of the ophthalmologists, only one child with DSN (out of nine) compared to all three children in the TN group had a thorough investigation of nystagmus. The nystagmus of all five children with DSN who were diagnosed with INS were reported to be associated with the DS and no other ocular conditions. Although there are no reports of children with DSN presenting with any ocular abnormalities, equally, there are no reports of specific investigations performed to confirm those claims. The following is a quote from a referral letter:

"*Horizontal nystagmus is a reasonably common association of Down's syndrome, so I have not advised any investigation*." (Ophthalmologist of P82 2018, Referral letter)

If the nystagmus is considered always to be simply associated with just DS, the visual impairment experienced by those individuals with DSN may be overlooked, and access to support services (e.g. registration as sight impaired, access to qualified teachers of the visually impaired, etc.) may less frequently be provided to these children than those presenting with nystagmus but not DS. Ideally, oculomotor assessments involving eye movement recording should be performed on all children with nystagmus whatever the associated condition, so that the characteristics of IN can be determined to confirm the diagnosis of IN.

6.4.2 Visual acuity

In Chapter 2, I found that the children with DSN had poorer mean binocular VA compared to previous studied of VA in typically developing children with INS (Fu et al. 2011). However, in the present study, I did not find any statistically significant difference between the BVA of children with nystagmus with and without DS. A possible explanation for this may be that the group of children with DSN consisted of those with INS and FMNS-like nystagmus (n=6), whereas all the children in TN group presented with ocular oscillation when observed during optometric assessment and all 9 children that produced good EMR data showed IN type waveform. In our study, acuity was measured using different tests compared to the tests used in the comparative study of Fu et al. (2011). In their study, VA in older children were measured using either the HOTV, EDTRS, Lea symbols or Allen symbols. The test used could have a confounding effect on the scores.

6.4.3 Waveform characteristics

Based on the optometric examination findings, 78.5% of children in the DSN and 94.1% in the TN group presented with ocular oscillation when viewing binocularly. Based on the results of the eye movement recording, INS type of waveform was seen in 75% of the children in the DSN group and 90.1% of the children in the TN group. The children with

FMNS-like waveform were all from the DSN group. However, the diagnosis of FMNS was not possible, as it would require EMR data with each eye occluded to determine if the direction of the nystagmus beat changed towards the viewing eye, which could only be achieved on one child (P34).

Based on the method of Dell'Osso and Daroff (1975), it seems that younger children in the TN group presented with pendular nystagmus, whereas the older children of this group presented with jerk type of waveform. However, no trend with age was seen in children with DSN. Pendular type waveforms are common in young children with nystagmus (Abadi and Dickinson 1986; Reinecke, Guo and Goldstein 1988; Theodorou et al. 2015). Based on the 'adaptationist approach' to classify the nystagmus waveform, most of the children with DSN and a majority of the children in the TN group presented with type 1 waveforms. FMNS type of nystagmus is common among the Down's syndrome population (Wagner, Caputo and Reynolds 1990; Averbuch-Heller et al. 1999). Three of the children with DSN presented with FMNS-like waveform.

This study found no significant difference in the nystagmus amplitudes and intensity between the two groups of children with nystagmus. EMR of the children with nystagmus was performed without restraining the head. This therefore allowed the children to view the stimulus using their adopted head position (i.e. null position). Therefore, the intensity of the nystagmus would have been at the lowest. Recording the eye movements without restraining the child's head gives us a picture of the characteristics of nystagmus and how the children would see in their daily activities.

6.5 Conclusion

This study was performed to determine whether there is any evidence that nystagmus is actually a different condition in children with DS compared to typically developing children. Although the EMR data are from a small sample, I found no evident difference in

the nystagmus of children with DS as compared to that of typically developing children. The VA results also revealed no statistically significant difference, suggesting that the presence of nystagmus has a similar effect on the vision of both groups of children in this study, with and without DS. Therefore, nystagmus investigation of IN in terms of assessment of eye movements and visual function should be performed on all children with nystagmus, including those with DS. The diagnosis of IN and the confirmation of the visual status of these children will give them equal access to the support services that they need.

CHAPTER 7 ACCURACY AND PRECISION OF EYE MOVEMENTS OF CHILDREN WITH AND WITHOUT NYSTAGMUS WITH AND WITHOUT DOWN SYNDROME DURING FIXATION AND SMOOTH PURSUIT

7.1 Introduction

Previous researchers have established that fixation and pursuit eye movements are present since early infancy in typically developing children with no other ocular conditions (Kremenitzer et al. 1979; Phillips et al. 1997; Hofsten and Rosander 1997; Luna and Velanova 2012; Pieh, Proudlock and Gottlob 2012). Studies of visual fixation in typically developing children have shown that fixation stability improves with age, with a reduced number of intrusive saccades (Ygge et al. 2005; Aring et al. 2007). Studies of smooth pursuit in typically developing children have shown that velocity gains ranged from 0.5 to 0.8 between the age of 1 and 3 years old (Rütsche et al. 2006; Pieh, Proudlock and Gottlob 2012) and reach adult values (mean gain ranging from 0.84 to 0.94) from 7 years old onwards (Katsanis, Iacono and Harris 1998; Salman et al. 2006; Vinuela-Navarro 2015).

Measurement of visual acuity requires the child to look at letter or picture optotypes, which are stationary on a visual acuity chart. Fixation, therefore, is required for the child to identify the letters or optotypes. The on-going oscillation of the eyes during fixation may have an impact on the visual acuity performance of children with nystagmus. Previous studies looking at eye movements during fixation in adults with nystagmus largely focused on determining the slow phase properties (Abadi and Worfolk 1989), foveation criteria (Chung and Bedell 1996), or the location of the null zone. Similarly, in children with nystagmus (with and without DS) fixation studies also largely focused on waveform classification (Theodorou et al. 2015; Weiss, Kelly and

Phillips 2016) or foveation criteria (Felius et al. 2011; Felius and Muhanna 2013; Felius, Beauchamp and Stager 2014). So far, one study has looked at the relationship between eye velocity and visual acuity deprivation in typically developing children with IN (Kelly, Phillips and Weiss 2018). The findings from this study were discussed in detail previously in Chapter 1, section 1.3.1.

As the eyes are constantly moving in individuals with nystagmus, it is difficult to know how accurate and precise the eye movements are when fixating on a stationary object. The accuracy and precision of eye movements during fixation in INS have only recently been studied in adults by McIlreavy (2016). The motivation for his study was to determine the accuracy and precision of eye movements during fixation at different gaze angles (±16º) along the horizontal and vertical axis. However, McIlreavy did not investigate whether visual acuity performance was related to the accuracy and precision of the eye movement. Since children with nystagmus (both with and without DS) have poor visual acuity, it is of interest in the present study to determine the accuracy and precision of eye movement of these children during fixation and its relation to their visual acuity as compared to children who do not have nystagmus.

Previous studies of smooth pursuit (SP) in nystagmus have largely involved adults, as mentioned earlier in Chapter 1. Only one study to date examined conjugate eye movements in children with DSN and showed that this group of children have "apparent pursuit superimposed on the slow phase of the underlying nystagmus" measured by "apparent pursuit gain" (Weiss, Kelly and Phillips 2016). The measure of SP performance in this study was gain. However, I have pointed out earlier in Chapter 5 that using velocity gain as a measure of smooth pursuit performance can only give information about the eye movement along one of the visual axes (i.e. horizontal or vertical) during a pursuit task, but not both simultaneously. This is because changes in position of a horizontal moving target, for example, only occur along the horizontal axis. Yet, changes in eye velocities can occur both the horizontally and vertically,

whether with or without nystagmus, as shown in Figure 7.1. Calculation of velocity gain for vertical eye movement would result in a gain of infinity, as the eye velocity would be divided by the vertical target velocity of 0º/s. In the case of fixational eye movements, velocity gain cannot be calculated at all, as the stationary target has a velocity of 0º/s on along both the horizontal and vertical axes.

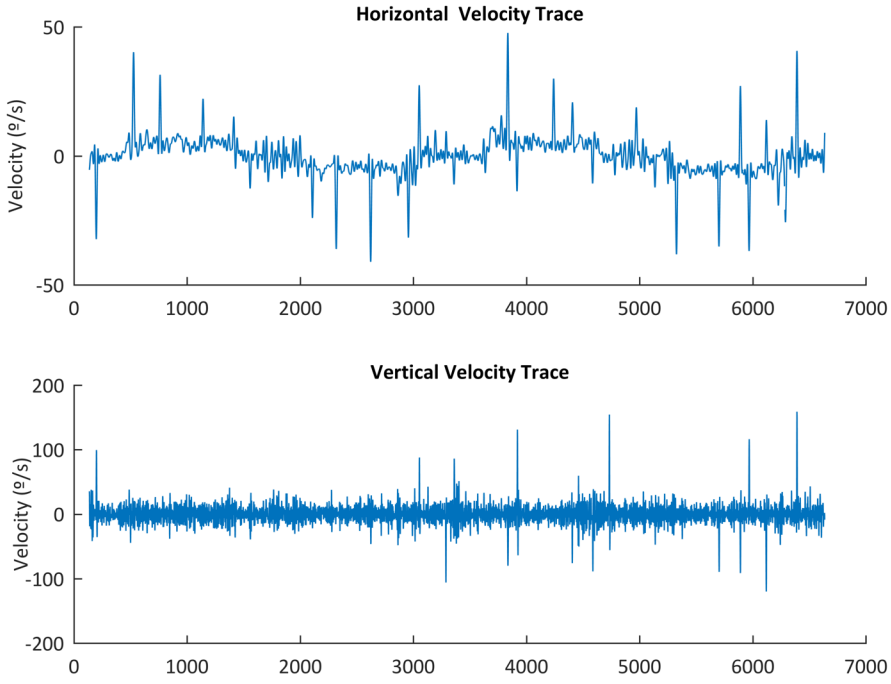

Figure 7.1 Velocity trace of a typical child with no nystagmus during a pursuit task. The eye velocities on both the horizontal and vertical axis changes throughout the task. Calculation of gain as a measure of eye movement performance can only be done for the horizontal axis, as the gain of the vertical axis would have the value of infinity.

The study by McIlreavy (2016) found that the accuracy and precision during fixation were better than during pursuit in typical adults with no nystagmus. However, adults with INS showed inaccurate and imprecise eye movements when following horizontally and vertically moving targets as well as when fixating a stationary target. To date, there are no available reports on the evaluation of accuracy and precision of eye movement during fixation and smooth pursuit in children with and without DS,

with and without nystagmus. Therefore, in this chapter, I will be using McIlreavy's method to measure the accuracy and precision of eye movement during rightward and leftward pursuit in children with Down's syndrome and nystagmus (DSN) and typically developing children with nystagmus (TN) and compared to velocity gain. The accuracy and precision of eye movements will also be measured during fixation at straight ahead position (0º). Additional to that, the data of both groups of children (DSN and TN) will be compared to that of children with DS without nystagmus (DS) and typically developing children without nystagmus (T).

7.2 Procedures

This study involved children with DSN (n=28) and TN (n=17) who previously participated in the study in Chapter 6. In addition to that, we also recruited children with DS and no nystagmus (DS, n= 20) and typically developing children with no nystagmus (T, n=20). Eye movement recording (EMR) was carried out on all children while they were performing the fixation and smooth pursuit tasks described in Chapter 5, section 5.3. The fixation task required the children to fixate a stationary stimulus displayed at the centre of the screen. The smooth pursuit task required the children to follow a horizontal moving stimulus (subtending 2º or 4º in size) that oscillated at a constant velocity of 6º/s and an amplitude of 20º, on the screen of the eye tracker. A two second fixation period was presented when the stimulus reached the end point on the left (-10º) and right (+10º) position of the screen). The children were instructed to "keep following the animal as it is going to change shape". To make sure the children were following the stimulus, they were asked to name the type of animal throughout the task. If and when the children were distracted from the task, the researcher then pointed to the stimulus on the screen to redirect their attention back to the stimulus. Binocular visual acuity (BVA) was also measured for all children using the procedure described in Chapter 5, section 5.2.2.

7.3 Analysis

7.3.1 EMR data

Good quality eye movement recording (EMR) data were extracted, processed and calibrated using the same procedure described in Chapter 5, section 5.4. The calibrated EMR data were then used to further analyse the eye movement performance during fixation and the SP task. The same EMR data of children with nystagmus used for the waveform analysis in Chapter 6 were used again for the analysis of the fixation task (i.e. fixation at straight ahead position). Examples of an eye trace of a child with and without nystagmus during SP are illustrated in Figure 7.2

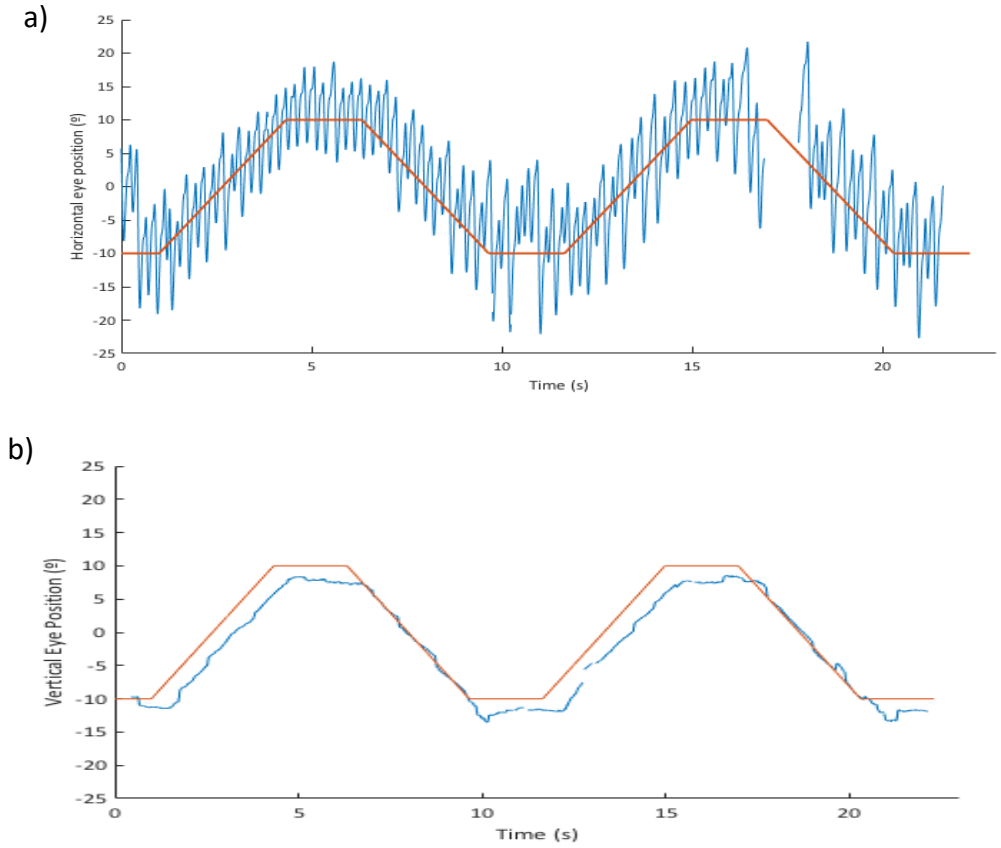

Figure 7.2 Examples of clean and calibrated eye trace of (a) a child with and (b) without nystagmus while pursuing a moving stimulus. Red line depicts position of the stimulus that moved 20º from left (negative values) to right (positive values) at 6º/s, with 2 seconds of fixation at ±10º position.

Eye velocities for both horizontal and vertical axes during the whole of both fixation and pursuit tasks were first calculated. Next, saccades were detected using the

saccade detection algorithm described in Chapter 5, section 5.4 and removed from the horizontal and vertical position and velocity data as shown in Figure 7.3. This means that, for nystagmus participants, only eye velocities during the slow phases were used to determine the accuracy and precision of eye movement during both fixation and smooth pursuit (Figure 7.4).

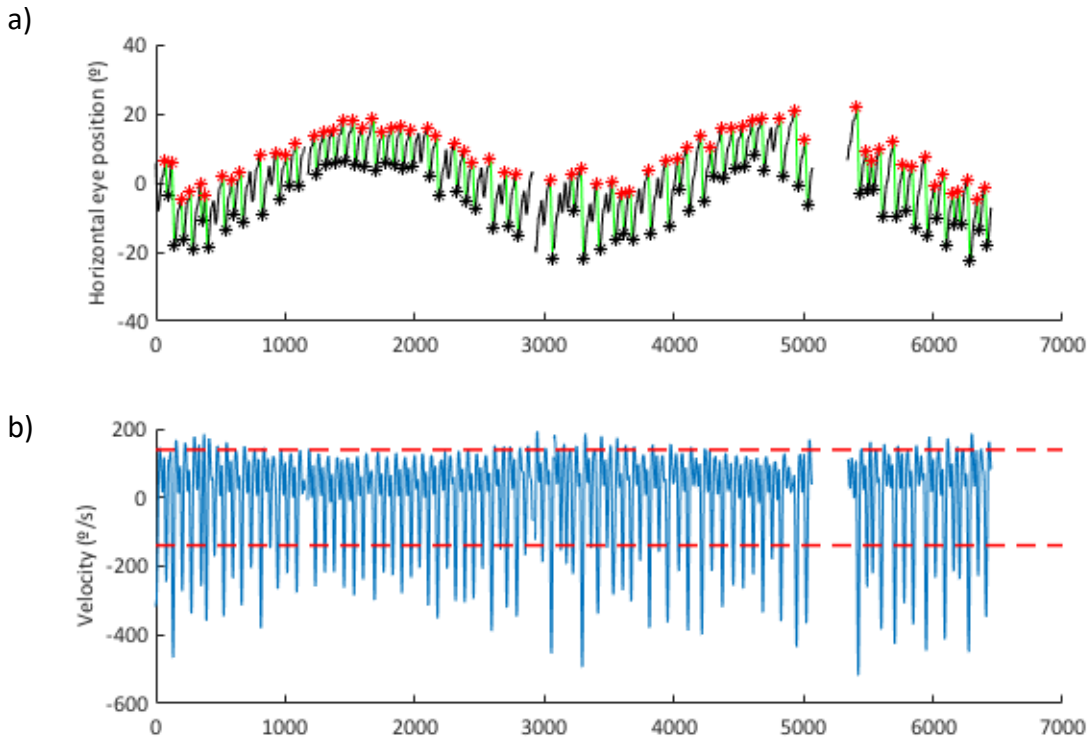

Figure 7.3 Eye trace (a) with detected saccades in horizontal eye position during the smooth pursuit task are highlighted in green. The saccade start and end points are marked with red and black asterisks. Dashed red lines represent ±1SD of the mean eye velocity

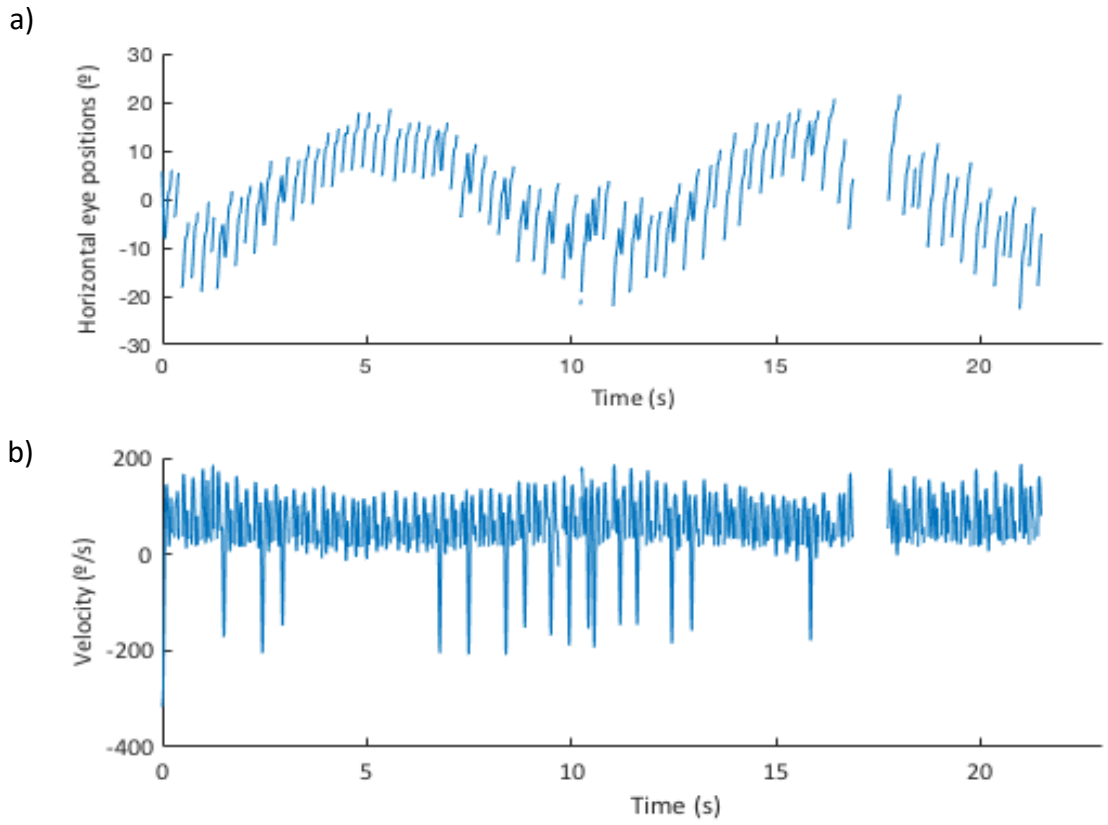

Figure 7.4 The detected saccades were removed from the (a) eye position and (b) velocity data for the subsequent probability density function (PDF) analysis

For the SP data, eye velocities at each of the four SP ramps and fixation positions were segregated (see Figure 7.5), after the saccades were removed. All fixation data were removed. Only data during SP were analysed. As there were two SP ramps for each target motion direction, eye velocities for the ramps that the target was moving in the same direction were concatenated. For example, eye velocities during ramps 1 and 3 were concatenated for rightward motion, whereas eye velocities during ramps 2 and 4 were concatenated for leftward motion. Therefore, each motion direction and fixation positions were only represented once.

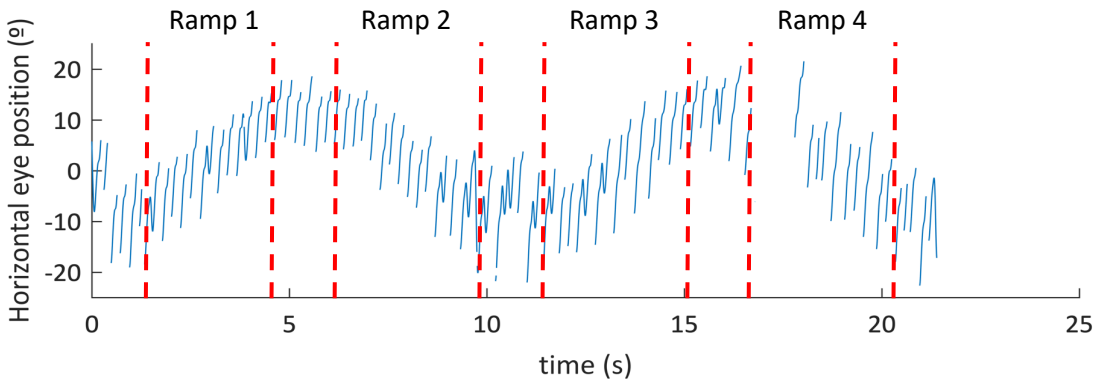

Figure 7.5 Segregation of the four smooth pursuit ramps (red dashed lines) from fixation data after removal of saccades

7.3.2 Velocity gain

Velocity gain for each direction of target motion (i.e. rightward and leftward) was calculated by dividing the eye velocity by the target velocity. This means that for rightward motion, the eye velocities were divided by +6º/s, and leftward motion, the eye velocities were divided by -6º/s.

7.3.3 PDF accuracy and precision

Target relative velocities are the velocities of the eye movements minus the target velocity. Target relative velocities during SP for each motion direction were therefore calculated by subtracting the target velocity (+6º/s for rightward motion and -6º/s for leftward motion) from the eye velocities. Target relative velocities during fixation were the same as the eye velocities because the target velocity was 0º/s. Figure 7.6 presents the relative velocities for each motion direction and fixation positions after concatenation. Probability density function (PDF) accuracy and precision were then computed using the method mentioned in Chapter 5, section 3.8. The reader is directed to the chapter for a full description of accuracy and precision. Accuracy will be expressed in terms of accuracy rho (the magnitude of the inaccuracy) and accuracy θ (the direction of the inaccuracy) in the following sections. Precision will be expressed in terms of area and shape factor for the PDF.

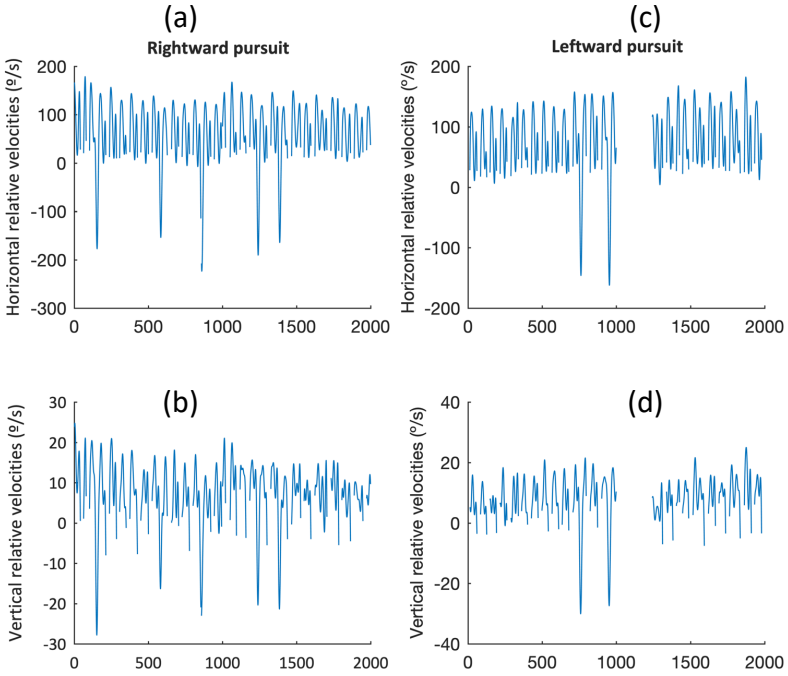

Figure 7.6 Example of concatenated horizontal and vertical target relative velocities during rightward (a and b) and leftward (c and d) pursuit

7.3.4 Statistical analysis

All statistical analyses were performed in IBM SPSS version 25. The distribution of the data was tested for normality using the Shapiro-Wilk test. Although some of the data were not normally distributed, parametric Analysis of Variance (ANOVA) were used to compare the means of the eye movement performance metrics (accuracy rho, precision, shape factor and velocity gain). This parametric test has been shown to be robust to data that are deviated from normality (Glass, Peckham and Sanders 1972; Lix, Keselman and Keselman 1996). A One-Way ANOVA was performed to compare the accuracy rho and precision during fixation at straight ahead position between the four groups of children. A two-way mixed ANOVA was conducted to investigate the impact of the type of condition (group) and the pursuit direction (rightward and leftward) on the smooth pursuit performance (accuracy rho, precision, shape factor and velocity gain) between the four groups of children. The Greenhouse-Geisser was applied on occasions when sphericity was violated. Post hoc testing was performed

using the Bonferroni adjustment for multiple comparisons. Fixation on the left (-10º) and right (+10º) during the SP task were not analysed. The reason for this was because the children's head were not restrained during the EMR recording. Therefore, the possibility that children turned their eyes/head into their null position when fixating the target cannot be excluded. Thus, we did not explore for differences in oculomotor behaviour at these different target locations.

Next, the mean direction of the inaccuracies (i.e. whether the eyes were leading or lagging the target) during SP for each group of children was determined by analysing accuracy θ. The data for accuracy θ has an angular scale, which is circular in nature. Using the usual linear statistics to analyse data of this nature would produce misleading results. For example, in Figure 7.7a, the arithmetic mean of the three data points at angles 10º, 30º and 350º would be 130º, while all the data points directed towards 0º, and so this result would be incorrect. The correct mean angle and direction is in fact 10º as shown by the red line in Figure 7.7b. These values were calculated using circular statistics toolbox for MATLAB (Berens 2009). The analysis produces the mean directions for the angular data (mean resultant vector, θr), length of the resultant vector (*r*) and the 95% confidence intervals (CI) of the mean resultant vector.

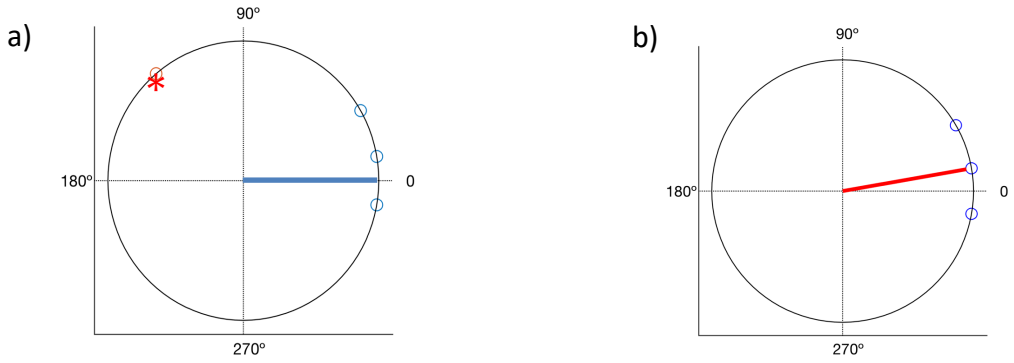

Figure 7.7 a) Data at 10º, 30º and 350º (blue dots on circles) all directing toward 0 (blue line) have an arithmetic mean of 130º (red asterisk) when calculated using customary linear statistics. b) The actual mean angle and direction is at 10º (red line) calculated using circular statistics. Adapted from Berens (2009)

The resultant vector length quantifies the spread of the data on the circle. The values of *r* can be between 0 and 1, whereby a value of 0 indicates that the points are placed uniformly on the circle and values that are close or equal to 1 show that the data are concentrated around the mean direction. As an example, the data in Figure 7.8a are distributed evenly on the circle at angles of 90º, 210º and 330º. Therefore, the *r* value for the dataset in Figure 7.8a is 0, whereas the *r* value for the dataset in Figure 7.8b is 0.96, with the mean direction of 180º.

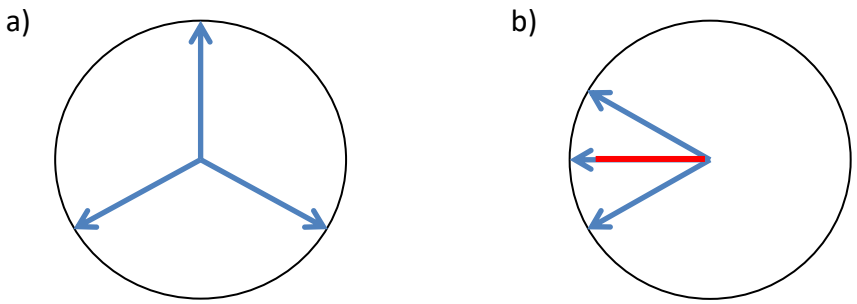

Figure 7.8 Examples of mean resultant vector (θr) and resultant vector length (r) adapted from Berens (2009). The data in (a) are distributed uniformly on the circle, producing a resultant vector length of 0. The data in (b) have a resultant vector length (red line) of 0.96 with θr = 180º

The uniformity of the distribution of the directional data on the circle was then determined using the Rayleigh z test. A significant p-value ($p<0.05$) indicates that the data are not uniformly distributed on the circle and, therefore, have a mean direction. Finally, the Watson-Williams test (Watson and Williams 1956; Berens 2009) was performed to compare the mean directions between rightward and leftward pursuit for all four groups of children, and to compare the mean directions between the four groups of children for both rightward and leftward pursuit.

7.4 Results: Fixation

7.4.1 Accuracy and precision during fixation

Fixation data were available for 41 children (10 DSN, 8 TN, 9 DS and 14 T). Examples of PDF during fixation at the center (0º) for children in the T and DS groups are illustrated in Figure 7.9. Figure 7.10 shows an example of the PDF results of children with DSN and TN. From the figures below, we can see that there is a clear difference in the shape of the PDFs between children with and without nystagmus. The PDFs of the children in the DS and T groups are more circular and smaller in size. In contrast, the PDFs of children in the DSN and TN group were more elongated, with the distribution of relative velocities stretched along one axis. Individual PDFs during fixation for each participant are attached in Appendices K through N. The mean of PDF accuracy and precision of all four groups of children are presented in Figure 7.11 and Figure 7.12. Note that the larger the value, the more inaccurate and/or imprecise the eye movements are.

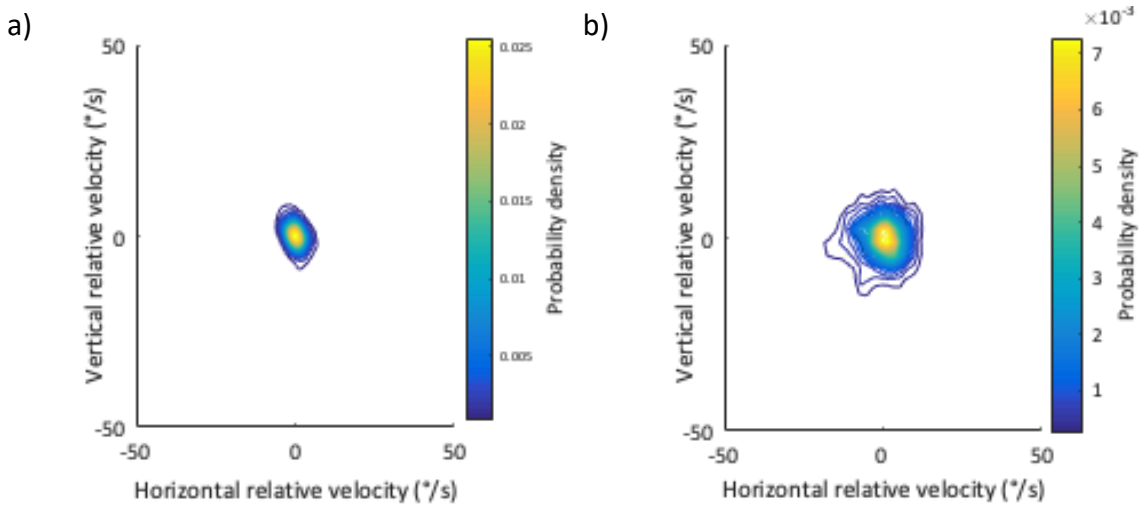

Figure 7.9 Probability density function examples of a typically developing child with no nystagmus, T (P47, accuracy = 0.36º/s, precision = 2.68 º/s^2) and a child with Down's syndrome and no nystagmus (P03, accuracy = 3.33º/s, precision = 729.77 º/s^2) during fixation at the center of the screen

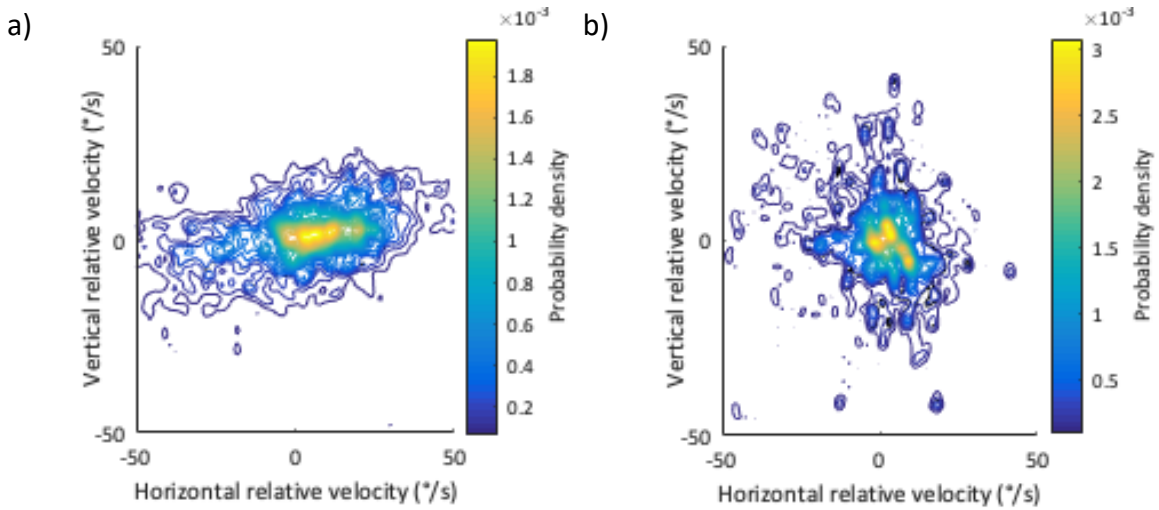

Figure 7.10 Probability density function example of (a) a typically developing child with nystagmus, TN (P59, accuracy = 8.51º/s, precision = 1848.34 º/s^2) and (b) a child with Down's syndrome and nystagmus, DSN (P31, accuracy = 1.2º/s, precision = 1126.83 º/s^2) during fixation

A One-way ANOVA between subjects was conducted to compare the accuracy and precision during fixation between the four groups of children. There was a significant difference in accuracy between the four groups of children [$F(3,37) = 3.23$, $p<0.05$]. Post hoc testing with the Bonferroni correction for multiple comparisons analysis showed that children in the TN group (mean = 8.42º/s, 95% CI [1.09, 5.11]) were significantly less accurate than children in the DS (mean = 0.75º/s, 95% CI [0.42, 1.07]) and T (mean = 0.59º/s, 95% CI [-0.07, 1.25]) groups. The accuracy of the DSN group (mean = 3.11º/s, 95% CI [1.09, 5.11]) was better than the TN group but poorer than the DS and T groups, although, no significant difference was shown ($p>0.05$).

Similarly, there was a significant difference in precision during fixation between the four groups of children [$F(3,37) = 5.30$, $p<0.01$]. Post-hoc comparisons indicated that the mean precision of children in the DSN (mean = 1137.07º/s^2, SD = 1224.37º/s^2) and TN (mean = 1076.24º/s^2, SD = 925.11º/s^2) was significantly poorer than children in the T group (mean = 118.60º/s^2, SD = 223.25º/s^2). However, there was no significant difference between the precision between the two groups of children with nystagmus

(p=1.00). There were no significant differences in precision between DSN and DS group (mean = 276.68º/s^2, SD = 254.93º/s^2) or between the DS group and either of the TN and T groups.

In summary, children in the T group were most accurate and precise when fixating, followed by children in the DS group, as compared with those with nystagmus. Of note is that there is no difference between the two nystagmus groups i.e. accuracy and precision in the DSN is not different from the TN group.

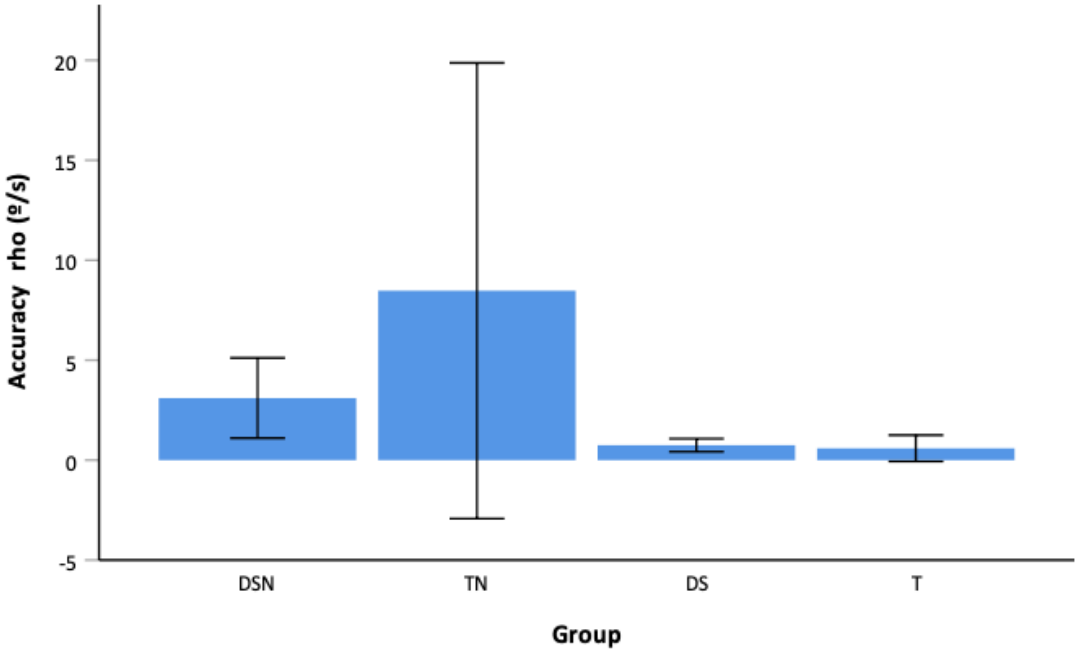

Figure 7.11 Mean accuracy rho for all four groups of children (Down's syndrome with nystagmus, DSN, typically developing children with nystagmus, TN, Down's syndrome, DS, and typically developing children with no nystagmus, T). Error bars depict 95% confidence intervals

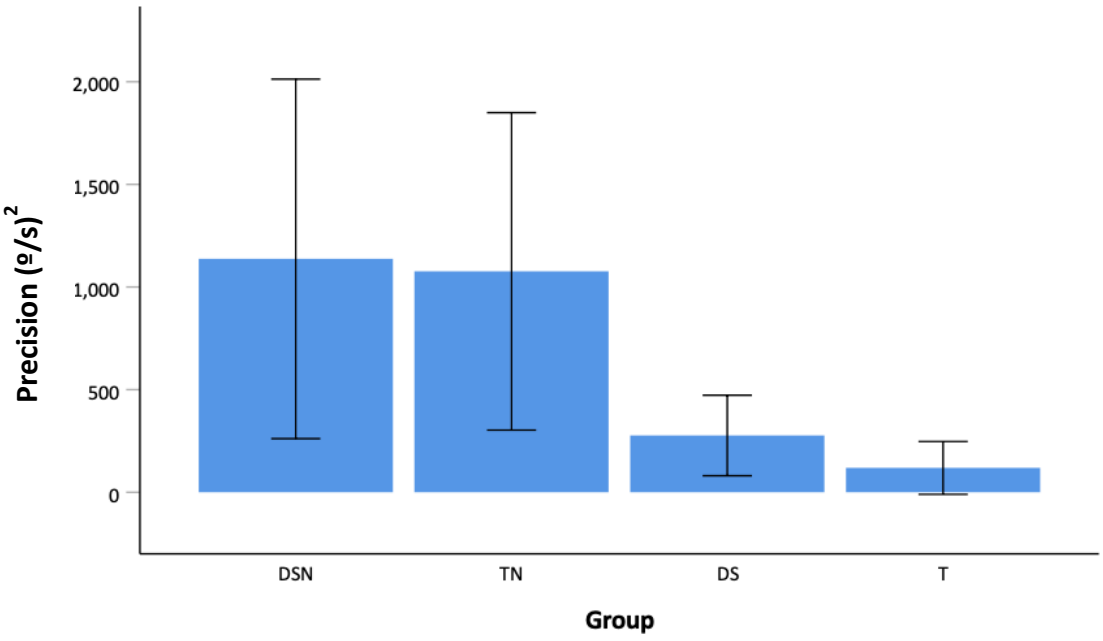

Figure 7.12 Mean precision for all four groups of children (Down's syndrome with nystagmus, DSN, typically developing children with nystagmus, TN, Down's syndrome, DS, and typically developing children with no nystagmus, T). Error bars depict 95% confidence intervals

7.4.2 Relationship between binocular visual acuity (BVA) and fixation performance

A Pearson's correlation coefficient was performed to determine if there was any association between BVA and the accuracy and precision during fixation. Table 7.1 summarises the mean and standard deviation (SD) of BVA for each group of the children with successful fixation data. The BVA of one child in the DS group (P42) was not available due to lack of cooperation. Recall that accuracy is the magnitude by which the center of the PDF isocontour extends relative to the target velocity. Greater values reflect a greater inaccuracy. Similarly, greater precision values reflect a higher variability of the eye velocities (i.e. greater imprecision). It was expected that there was a positive correlation between BVA and the eye movement performance metrics. However, no significant relationship was found between BVA and fixation performance in any of the four groups of children as shown in Table 7.2. Altogether, accuracy and precision of eye movements do not appear to relate to visual acuity. This seems to go against the inter-observer trend noted by Chung and Bedell (1995) who

found that greater intensity (a sort of measure of precision) was associated with lower acuity However, the study involved adults, therefore the relationship may not be applicable to children. Furthermore, there were only two participants in their study, i.e. far fewer than in the present study.

Group	Binocular visual acuity (logMAR)	
	Mean	SD
DSN	0.61	0.31
TN	0.54	0.39
DS	0.80	0.31
T	0.22	0.19

Table 7.1 Mean and standard deviation (SD) of binocular visual acuity for children in each group with successful fixation data

	Group	n	*r*	p-value	R^2
Accuracy	DSN	10	-0.24	0.49	0.06
	TN	8	0.19	0.69	0.04
	DS	9	0.22	0.59	0.05
	T	15	-0.18	0.55	0.03
Precision	DSN	10	-0.31	0.39	0.09
	TN	8	-0.23	0.98	0.05
	DS	9	0.36	0.74	0.13
	T	15	-0.15	0.68	0.02

Table 7.2 Results of the Pearson's correlation coefficient for each group of children. No significant relationship between BVA and fixation performance

7.4.3 Fixation performance vs nystagmus intensity

A Pearson's correlation coefficient was also performed to determine if there was any association between nystagmus intensity and either the accuracy and precision or both during fixation for each group of children with nystagmus. Table 7.3 summarises the results for children in both the DSN and TN group. It was predicted that a

significant association would exist between nystagmus intensity and accuracy and precision. However, a significant positive correlation was only found in the TN group of children. This indicates that in the TN group, as the nystagmus intensity increases, the magnitude of the inaccuracy also increases, as expected.

	Group	n	*r*	p-value	R^2
Accuracy rho	DSN	10	-0.23	0.57	0.05
	TN	8	0.88	<0.01	0.78
Precision	DSN	10	0.43	0.21	0.19
	TN	8	0.23	0.45	0.09

Table 7.3 Results of Pearson's correlation testing the association between eye movement performance during fixation (accuracy and precision) and nystagmus intensity

However, there was no significant correlation between the nystagmus intensity and precision in either group of children with nystagmus. This finding was unexpected as previous studies involving adults with IN found a relationship between intensity and precision (McIlreavy 2016). One reason for this difference in findings could be the low data samples that were used to analyse fixation. Recall that in some of the participants with nystagmus in this study, the fixation analysis was limited to the fixation data before the SP task began, because not enough data were available from the fixation task. In addition to that, the fixation data of the children in this study were more variable.

7.5 Results: Smooth pursuit

7.5.1 Velocity gain

Good quality EMR data for pursuit were available for 51 children (11 DSN, 10 TN, 10 DS and 20 T). The mean and 95% CI for rightward and leftward velocity gain of each group of children are illustrated in Figure 7.13. Results of the two-way repeated mixed

ANOVA showed no significant main effect of target direction on the velocity gain within each group of children ($F(1,3) = 3.46$, $p= 0.07$). However, there was a significant main effect of type of condition (DSN, TN, DS and T) on velocity gain ($F(1,3) =5.81$, $p<0.01$). The Bonferroni correction for multiple comparisons analysis showed a significant difference in the velocity gain ($p<0.01$) between children in the TN group (mean=4.85, 95% CI [3.12,6.67]) and children in the T (mean=0.83, 95% CI [0.78,0.87]) and DS (mean=1.33, 95% CI [0.81, 1.84]) groups. The gain of children in the DSN group was better than that of children in the TN group but poorer than the DS and T group, although it was not significant (TN, $p=0.46$; DS, $p=1.00$ and T, $p=0.31$). The large variability of the gain values for both groups of children with nystagmus could be explained by the variation in nystagmus intensity. Since the whole of the slow phases were used to determine the gain in these groups of children, low intensity nystagmus would produce lower gain values compared to those with high intensity nystagmus. The gain of children with nystagmus in this study were also higher than those reported in a previous study of children with DSN (Weiss, Kelly and Phillips 2016) .

In summary, the most accurate pursuit was by children in the T group, followed by the DS group and then those with nystagmus (DSN and TN, respectively). Although the IN oscillation is typically unidirectional, i.e. it may be right or left beating (if jerk), there were no significant differences between leftward or rightward pursuit. The gain values of the children in the T group were consistent with gain values of typically developing children reported by previous studies (Salman et al. 2006; Rütsche et al. 2006; Vinuela-Navarro 2015)

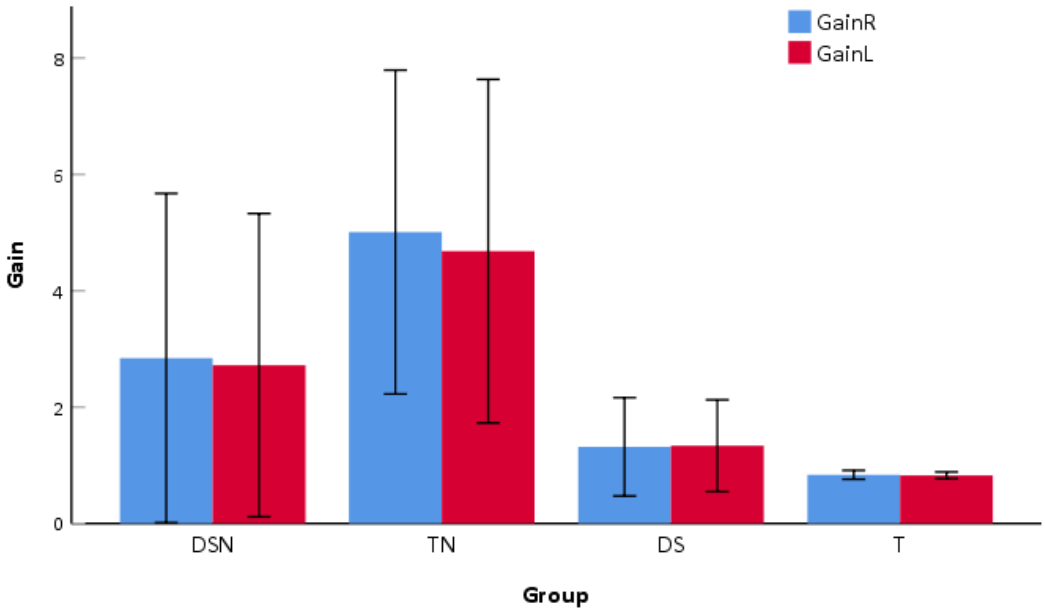

Figure 7.13 Mean and 95% CI of rightward (blue bars) and leftward (red bars) velocity gain during pursuit for children with DS and nystagmus (DSN), typically developing children with nystagmus (TN), children with DS without nystagmus (DS) and typically developing children without nystagmus (T)

7.5.2 Accuracy rho

Figure 7.14 and Figure 7.15 are examples of the PDF of a child performing rightward pursuit eye movement for each group of participants without and with nystagmus respectively. Individual PDFs for each participant are attached in Appendices O through R. Similar to fixation, the PDFs of children in the T and DS groups are more circular than that of children in the DSN and TN group, which were more elongated along one axis.

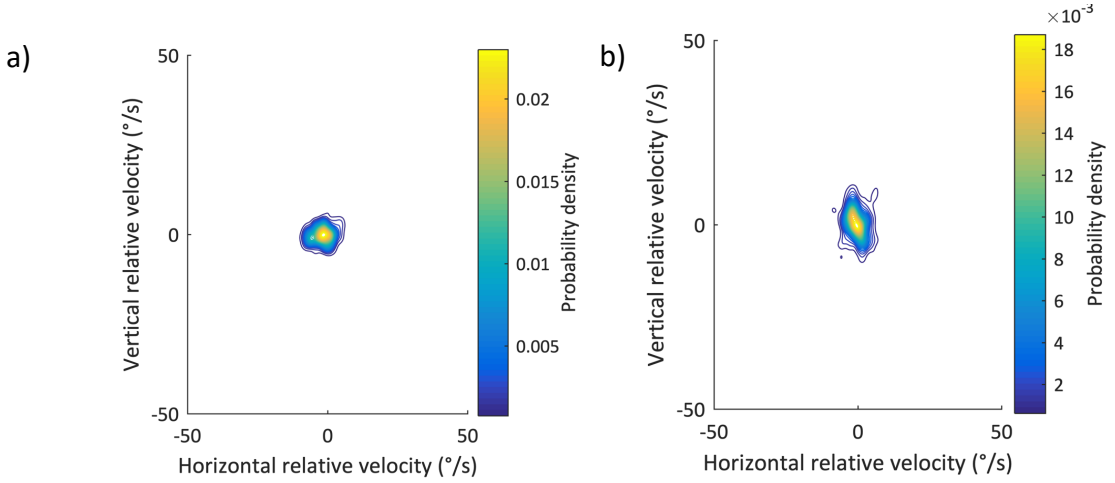

Figure 7.14 Illustration of PDF of horizontal and vertical target relative velocities during rightward pursuit of a) typically developing child (P47) and b) child with DS (P03) without nystagmus

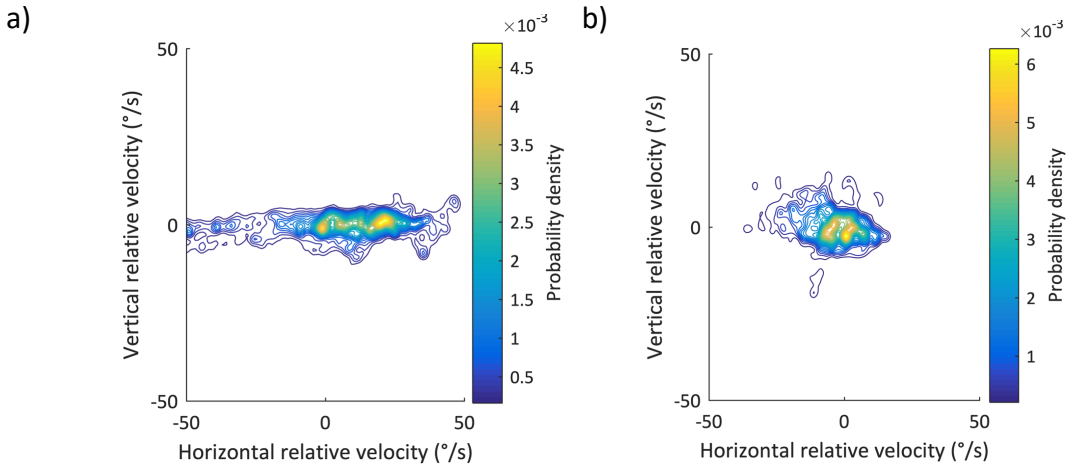

Figure 7.15 Illustration of PDF of horizontal and vertical target relative velocities during rightward pursuit of a) typically developing child (P71) and b) child with DS (P31) with nystagmus

The mean and 95% CI of the accuracy rho and precision, respectively, for rightward and leftward pursuit for all four groups of children are illustrated in Figure 7.16. Results of the two-way repeated mixed ANOVA showed no significant main effect of target direction on the accuracy rho within each group of children ($F(1,3) = 0.005$, $p = 0.94$). There was also no significant main effect of the type of condition (DSN, TN, DS, and T) on accuracy rho ($F(1,3) = 2.45$, $p=0.07$). However, there was significant interaction between condition and pursuit direction ($F(1,3) = 3.25$, $p<0.05$).

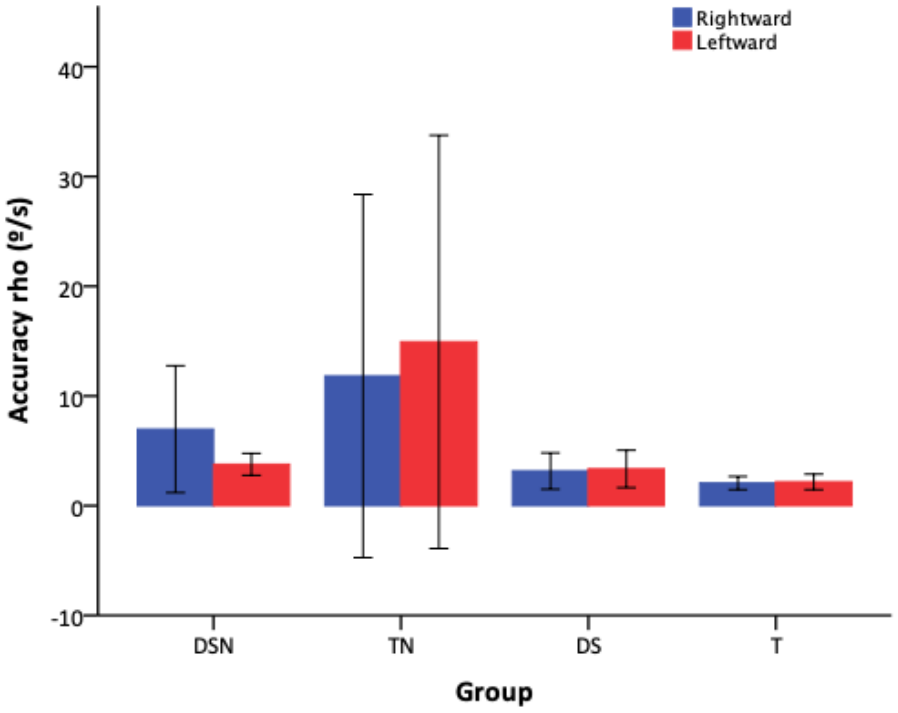

Figure 7.16 Mean accuracy rho for rightward and leftward pursuit of all four groups of children (Down's syndrome with nystagmus, DSN; typically developing children with nystagmus, TN; Down's syndrome no nystagmus, DS and typically developing children with no nystagmus, T). Error bars denote 95% confidence interval

The trend of accuracy rho obtained in this study was similar to the velocity gain results. This is not surprising as both are measuring accuracy. Children in the T group were most accurate when pursuing, followed by the DS and DSN group respectively. The least accurate were children in the TN group. Note that once again, there was no significant difference between children in the DSN and TN group. Although the trends were similar, the interpretation of accuracy rho contradicts that of velocity gain. The velocity gain results suggest that the eyes of both groups of children with nystagmus were leading the target (gain of >1). However, interpretation of accuracy rho requires the examination of accuracy θ (see next section), which suggests that the eyes of the children with nystagmus were actually lagging the target. These differences can be explained by the fact that accuracy was determined by using only the 68% of the most

common eye velocities. Gain on the other hand, was determined by calculating the mean velocity of the entire slow phase, which can be skewed by high velocities.

7.5.3 Accuracy θ

The distributions of accuracy θ data of rightward and leftward pursuit for each group of children are illustrated in Figure 7.17 through Figure 7.20. The small blue circles represent the direction of the inaccuracies relative to the target velocity (center of the circles). For rightward pursuit, any values falling on the left half of the circle indicate that the eyes were moving slower than the target (lagging) and vice versa. In contrast, if the values fall on the right half of the circle, the eyes were moving faster than the target (leading). The opposite can be said for leftward pursuit, where values that fall on the left half of the circle suggest the eyes were moving faster than the target, and vice versa. The plots in the following figures indicate that the eyes were lagging behind the target in both directions for all of the children in the DS and T groups, and a majority of the children in the DSN and TN groups.

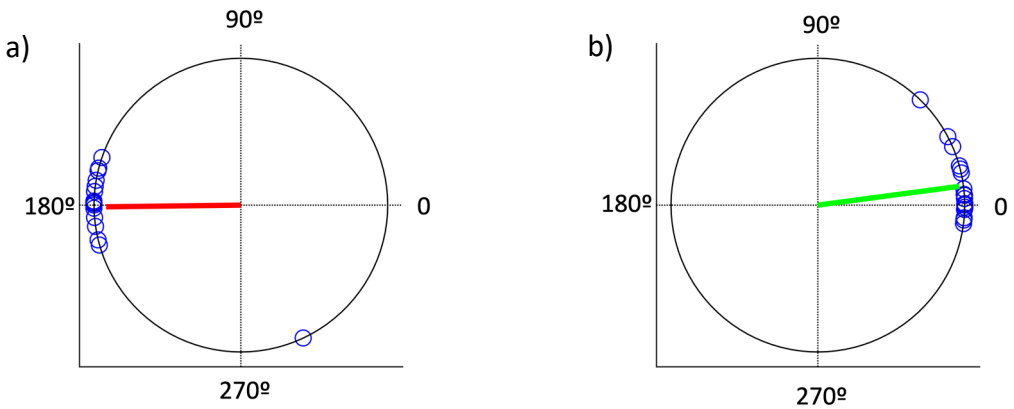

Figure 7.17 Accuracy θ data of a) rightward and b) leftward pursuit for typically developing children without nystagmus (T)

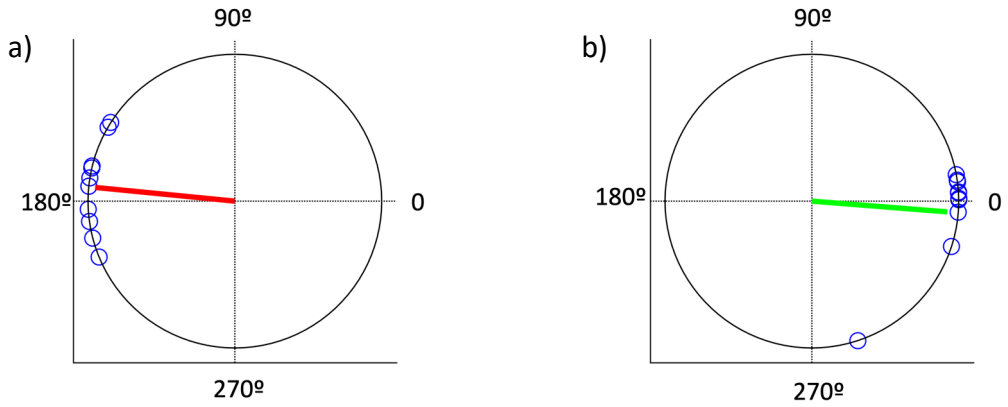

Figure 7.18 Accuracy θ data of a) rightward and b) leftward pursuit for children with Down's syndrome without nystagmus (DS)

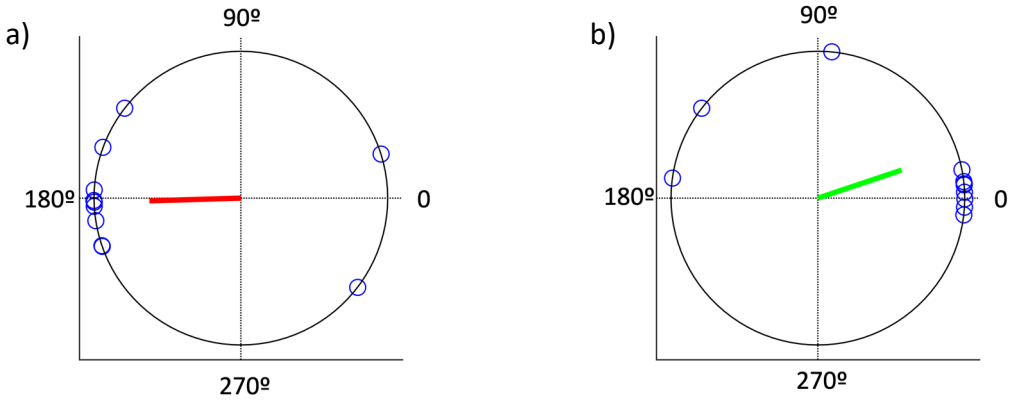

Figure 7.19 Accuracy θ data of a) rightward and b) leftward pursuit for children with Down's syndrome and nystagmus (DSN)

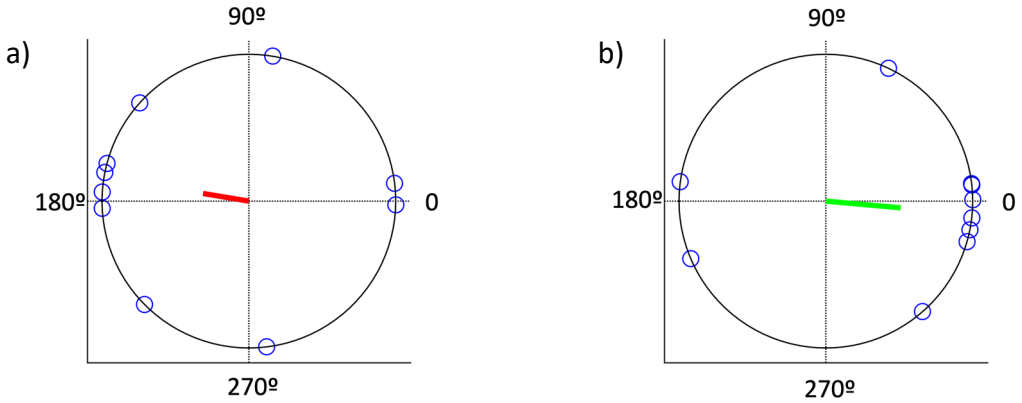

Figure 7.20 Accuracy θ data of a) rightward and b) leftward pursuit for typically developing children with nystagmus (TN)

A summary of the circular statistics results is shown in Table 7.4 and Table 7.5. The resultant vector lengths (r) for children in DSN and TN group were shorter (closer to 0) than children in the DS and T group. This outcome is due to the fact that accuracy θ data of the children with nystagmus were more spread out on the circle away from the mean direction (see Figure 7.19 Figure 7.20). Notice that the data of both groups of children with nystagmus are located on both halves of the circles, whereas the data of children in the DS and T group were all located on either the right or left side of the circle. This signifies that, although most of the children with nystagmus were moving more slowly than the target, there were some that were moving faster than the target.

However, results of the Rayleigh test were significant for all groups of children during both pursuit motions, except for children in the TN group during rightward pursuit. This means that the data for children in the TN were more uniformly distributed on the circle during the rightward pursuit suggesting that some children were leading the target.

Group	r	θr (radians)	95% CI	Rayleigh z	p-value
DSN	0.62	-3.11	0.68	4.28	<0.05
TN	0.31	2.98	-	1.00	0.38
DS	0.96	3.04	0.21	9.15	<0.01
T	0.92	-3.13	0.20	16.83	<0.01

Table 7.4 Results of circular statistics on accuracy theta data of rightward pursuit for each group of children

Group	R	Mean direction (θr)	95% CI	Rayleigh z	p-value
DSN	0.60	0.32	0.72	3.97	<0.05
TN	0.51	-0.09	0.99	2.60	0.07
DS	0.93	-0.07	0.28	8.56	<0.01
T	0.97	0.13	0.11	18.93	<0.01

Table 7.5 Results of circular statistics on accuracy theta data of leftward pursuit for each group of children

The Watson-Williams test was also performed to compare the mean direction between each group of children for rightward and leftward pursuit. There was no significant difference in the mean direction between the four groups of children for both rightward pursuit ($F(50)=0.11$, $p=0.95$) and leftward ($F(50)=0.69$, $p=0.56$) pursuit. This indicates that the eyes of all four groups of children were moving more slowly than the target for both target motion.

Altogether, these findings demonstrate that in general, the eye velocities of the children involved in this study were moving more slowly than the target. When the results of accuracy rho and theta are examined together, accuracy would be a more appropriate measure for eye movement performance. Furthermore, accuracy provides information for eye performance for both horizontal and vertical axes whereas gain does not.

7.5.4 Precision

Figure 7.21 exhibits the mean and 95% CI of precision during rightward and leftward pursuit of all four groups of children. Although it seems that the precision was poorer during rightward pursuit for all groups of children, except the DSN group (poorer precision during leftward pursuit), there was no significant main effect of target

direction on precision within each group of children ($F(1,3) = 0.05$, $p= 0.94$). There was, however, a significant main effect of type of condition on precision ($F(1,3) =7.44$, $p<0.01$). Post hoc analysis showed a significant difference ($p<0.01$) in precision between children in the TN group and DS and T groups. Children in the TN group showed poorer precision during pursuit (Rightward mean = 1153.45º/s^2; Leftward mean = 1218.96º/s^2) compared to children in the DS (Rightward mean = 295.55º/s^2; Leftward mean = 196.50º/s^2) and T group (Rightward mean = 90.06 º/s^2; Leftward mean = 78.27º/s^2). There was no significant difference between the TN and DSN group ($p=0.66$). No significant interaction was shown between condition and pursuit direction. The precision of eye movements of the children in the DSN, TN and DS groups were much poorer than that of adults with IN (approximately 590º/s^2 rightward and 650º/s^2) reported by McIlreavy (2016). Similarly, children in the T group had poorer precision than typical adults (approximately 0.6º/s^2 for both rightward and leftward motion) reported in the same study.

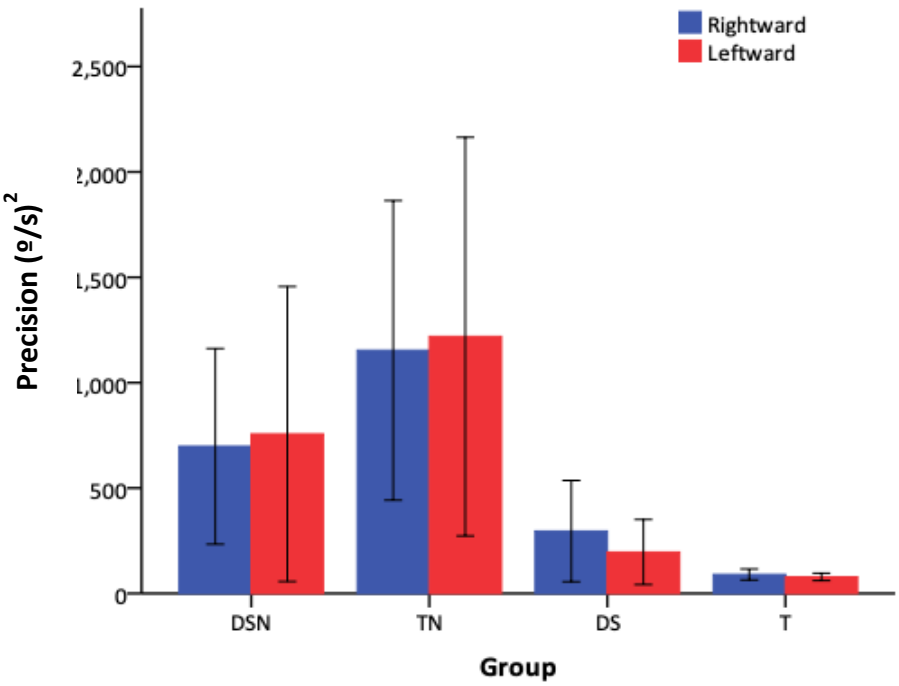

Figure 7.21 Mean precision during rightward and leftward pursuit of children in all four groups (Down's syndrome with nystagmus, DSN; typically developing children with nystagmus, TN; Down's syndrome without nystagmus, DS and typically developing children without nystagmus, T). Error bars indicate 95% confidence intervals

In summary, children in the T group showed the most precise pursuit, followed by the DS and DSN groups. Children in the TN group had the most imprecise pursuit. However, there was no significant difference between the DSN and TN groups.

7.5.5 Shape factor

The shape factor (a ratio between the minor and major axis) of the PDF was calculated to determine whether the imprecision lies along a major axis (see Chapter 5, section 5.7). A smaller shape factor than 1 indicates a more asymmetric spread of precision along one axis (i.e. the major axis). Figure 7.22 exhibits the distribution of the shape factor for all four groups of children. No significant main effect of target direction on shape factor within each group of children was shown ($F(1,3) = 0.04$, $p= 0.84$). There was a significant main effect of type of condition on the shape factor ($F(1,3) =10.91$, $p<0.01$). Post hoc testing revealed that the mean shape factor of children in the DSN (Rightward mean = 0.56; Leftward, mean = 0.47) and TN (Rightward mean = 0.35; Leftward, mean = 0.0.36) groups were significantly smaller ($p<0.01$) than the T (Rightward mean = 0.69; Leftward mean = 0.69) group. The mean shape factor of the TN group was also significantly smaller ($p<0.01$) than the DS group (Rightward mean = 0.59; Leftward mean = 0.69). However, there were no significant difference between DS group and the DSN and T groups. These findings indicate that, for children in the DSN and TN group, the imprecision of the eye movements occurs along the major axes, whereas, the imprecision of the eye movements of children in the DS and T group occurs almost equally along both horizontal and vertical axes. This was expected, as the ocular oscillation in nystagmus is greater along one axis. No significant interaction was shown between condition and pursuit direction ($F(1,3) = 1.32$, $p= 0.28$).

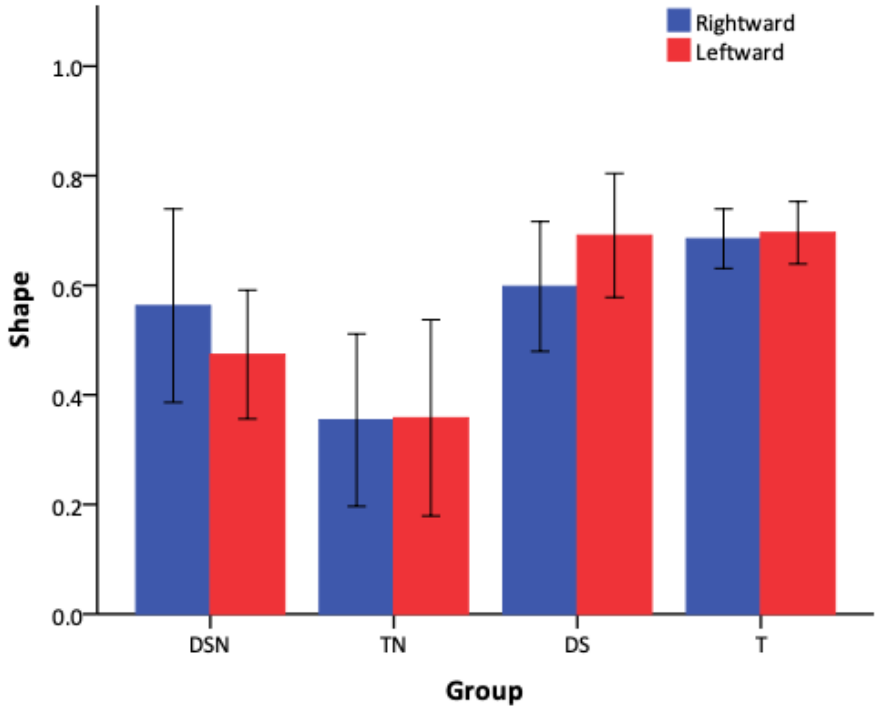

Figure 7.22 Mean shape factor of the PDF for each group of children (Down's syndrome with nystagmus, DSN; typically developing children with nystagmus, TN; Down's syndrome without nystagmus, DS and typically developing children without nystagmus, T) during rightward and leftward pursuit. Error bars indicate 95% confidence intervals

In summary, children in the TN group showed the smallest shape factor, followed by children in the DSN, DS and T groups. The smaller shape factor of children in the TN and DSN groups compared to the DS and T groups suggest that, the imprecision of the eye movements of children with nystagmus occur almost along the major axes, which can be attributed to the ocular oscillation that is usually greater along one axis.

7.6 Discussion

Previous studies of fixation on children with nystagmus with and without DS focused on determining the type of oscillation (Abadi and Bjerre 2002; Weiss, Kelly and Phillips 2016) or the presence and duration of foveations (Felius et al. 2011; Felius and Muhanna 2013; Felius et al. 2014). In this study, the accuracy and precision of eye movements during fixation in children with nystagmus with and without DS were examined. Results showed that typically developing children with nystagmus have

poorer accuracy and precision during fixation and pursuit compared to both groups of children who do not have nystagmus. However, there was no significant difference in accuracy and precision during fixation and smooth pursuit between the children in the DSN and the TN group. Although the eye movement performance of children with DSN was poorer than the children without nystagmus (DS), this difference was not significantly different. A possible explanation for this may be that the type of nystagmus of the children the DSN group consisted of both the INS and FMNS-like waveform. Under binocular viewing, the eyes are almost stable in FMNS (Abadi and Scallan 2000). Therefore, the eye movements would be expected to be similar to those who do not have nystagmus. The combination of poor accuracy and precision of children with INS type waveform and good accuracy and precision of children with FMNS-like waveforms may have contributed to the non-significant findings. Due to the small sample size, I decided to include all the children in the DSN group in the analysis regardless of the nystagmus type. Increasing subject numbers and separating the children according to the type of nystagmus may produce a significant result.

The findings from this study also showed that nystagmus intensity correlates with accuracy of fixation of children in the TN which is consistent with the findings of adults with IN (McIlreavy 2016). However, as in the present study, McIlreavy (2016) also showed that there was no significant correlation between intensity and accuracy and precision in individuals with low intensity nystagmus.

To determine the smooth pursuit performance of children with nystagmus with and without DS, I first looked at the velocity gain of these children during pursuit compared to children without nystagmus. The present study found that children in both the DSN and TN groups have a mean velocity gain higher that those without nystagmus (2.78±3.95 and 4.85±3.91 respectively). Once again, a significant difference was only seen between children in the TN group and children in the DS and T groups. The high velocities of the eyes caused by the oscillation explain the high value of gain in the

group of children with nystagmus. However, it is important to point out that these high velocity slow phases do not necessarily constitute normal pursuit. For example, the average slow phase velocity of the children with nystagmus in this study was 26.25º/s. Therefore, if the eye velocity was divided by the target velocity of 6º/s, the value of the gain would be 4.37. This suggests that the eyes of individuals with nystagmus move faster than the target, which in essence is correct.

Reported pursuit gains for adults with nystagmus vary. Some papers report gains of between 0.3 to 0.75 (Yamazaki 1978) or have been reported as normal (Dell'osso 1986; Dell'Osso and Jacobs 2013). In those studies reporting normal gain, they did not use the entire slow phase, but fitted a line of best fit through the foveation positions. In this study, I used the whole of the slow phase. However, McIlreavy (2016) have pointed out the limitations of using this approach, and pioneered the PDF accuracy and precision method to assess eye movement performance that I have used in this thesis.

The accuracy of eye velocity during fixation in children with DSN in the present study was found to be better than that of adults with IN (approximately 6.5º/s) as reported by McIlreavy (2016). Once again, the mixture of nystagmus type in the DSN group of children may explain this surprising finding. All the adults involved in the study by McIlreavy had IN, with a majority having jerk waveforms. Hence, the nystagmus would have been more intense compared to some of the children in the DSN group who presented with FMNS. However, interestingly, the accuracy of children in TN group in this study who all had IN were poorer than the adults in McIlreavy's study. In fact, both groups of children with nystagmus in this study showed poorer precision than the adults with IN reported in McIlreavy's study. This could suggest that children with nystagmus, whether with or without DS do not regulate their eye velocities as well as adults with IN. It can be argued that differences in the target size and type used may be a factor that contributed to the difference in findings. In contrast to the small (0.4º)

standard dot used in McIlreavy's study, the present study used either a 2º or 4º animated stimulus in both pursuit and fixation task. However, I have shown in Chapter 3 that there was no significant difference in the precision (determined by the total area of eye positions during fixation) between different type and size of stimulus. Vinuela-Navarro et al. (2017) also found no significant difference in smooth pursuit gain between stimulus size of 1º and 2º.

Due to the limitations of attention and cooperation, I only investigated the performance during horizontal pursuit at one velocity and amplitude. However, it has been shown that different target frequencies (acquired by combining different pursuit amplitudes and target velocities) can affect the smooth pursuit performance in adults with IN (McIlreavy 2016). Since objects in the real world move at a variety of velocities and direction, it would be beneficial to investigate the smooth pursuit performance of children with nystagmus with and without DS at different target frequencies and direction, or using more complicated patterns of motion, such as random sinusoids. This may have the added benefit of understanding the real-world difficulties faced by these individuals. For example, when in clinic, participants would ideally have unlimited time to repeatedly foveate a target (i.e. the letters or symbols on the acuity chart). However, if this target was moving, participants may not be able to appropriately foveate it; by the time their fast phase redirects their eye, the target may already have moved. Thus, the results of such study may highlight how VA overestimates visual function in those with nystagmus. Unfortunately, it was not possible to carry out the experiment in the present study due to the difficulties discussed earlier. Nonetheless, the present study has shown that the accuracy and precision of eye movements in children with nystagmus, both with and without DS, when following a target moving at a constant velocity, which has not been shown before. Therefore, it is only logical to carry out the above experiment in future studies.

The results for fixation may indicate the quality of foveation, with lower accuracy and lower precision values (i.e. better accuracy and precision) being associated with better quality foveation (Liesberger et al. 1981).

7.7 Conclusion

This study investigated the accuracy and precision of eye movements in children with nystagmus during fixation and pursuit. Our findings showed that both groups of children with nystagmus in this study (DSN and TN) were unable to match the target velocities accurately compared to children without nystagmus (DS and T) both during fixation and smooth pursuit. Both groups of children with nystagmus also showed poorer precision during both eye movement tasks, suggesting that they were unable to regulate their eye velocities as well as children who do not have nystagmus. However, children in the DSN group showed a slightly better eye movement than children in the TN group, although this was not significant and may well be caused by the pooling of children with INS and FMNS type waveform in the same DSN group. The fact that there is no significant difference between the two groups with nystagmus suggests that nystagmus has the same effect on the eye movement performance in typical children and those with DS.

CHAPTER 8 GENERAL DISCUSSION AND FUTURE WORK

8.1 Introduction

Although a common condition in children with DS, nystagmus seems to be overlooked by eye care practitioners in this population of children. The aim of this thesis was to determine whether nystagmus was the same or a different condition in children with DS compared to typically developing children and how nystagmus affects visual acuity and eye movement performance during fixation and smooth pursuit. The findings would then give insight as to whether children with DSN should be given the same management for their nystagmus as their typical counterparts. The major findings of each chapter in the thesis and ideas for future work are summarized in the following sections.

8.2 Visual and refractive development of children with DS and nystagmus

In this retrospective study, I aimed to determine the development of visual acuity (VA) and refractive error of children with DSN (Chapter 2). The findings showed that binocular VA of children with DSN deviates from that of children with DS without nystagmus after early infancy and remains poorer throughout childhood. VA of children with DSN was also found to be poorer when compared to published norms (Fu et al. 2011) of VA of typically developing children with nystagmus.

This study also found that children with DSN had a higher prevalence of myopia than children with DS without nystagmus. Previous studies have shown that there is a strong association between nystagmus and heart defects in children with DS (Bromham et al. 2002; Kranjc 2012a). Bromham et al. (2002) also found a strong association between heart defects and myopia in this group of children. Therefore, it is not surprising that there is a higher prevalence of myopia in children with DSN.

There was no difference in prevalence of astigmatism between children with DSN and DS, which is in contrast to typically developing children with nystagmus who had higher prevalence of astigmatism compared to their counterpart without nystagmus. This could be explained by the fact that children with DS in general are known to have high prevalence of astigmatism (Woodhouse et al. 1997; Haugen, Høvding and Lundström 2001). Therefore, having nystagmus does not make it any more likely for children with DSN to develop astigmatism.

8.3 Success rates

The experimental study began with the development of techniques and stimuli appropriate for young children (Chapter 3). Animated stimuli with facial features of animals were designed and tested to attract the attention of young children during EMR. The quality of EMR data in adults with and without nystagmus while fixating on two different stimulus types (animated and non-animated) and sizes (2º and 4º) were compared by looking at the mean total area of eye positions during fixation between the two groups. The variability of eye position was quantified by identifying the area in which at least 68% (equivalent to the mean ± 1SD of the normal distribution) of fixations occur (Crossland and Rubin 2002; Bellmann et al. 2004; Crossland, Culham and Rubin 2004; Cherici et al. 2012). The area covering 68% of fixation positions was then calculated. The bigger the area, the less precise the eye movements were (i.e. poorer quality data). There was no significant difference between the mean total area of eye positions between both stimulus types and sizes for both adults with and without nystagmus.

Eye movement recordings (EMR) in young children with nystagmus and special needs presented with many challenges (Chapter 3). It is clear that the experience of working with young children is essential; techniques improved as the study progressed. For example, it was discovered that the eye tracker was having difficulties tracking the eyes of some children when the black background was being used in the eye

movement tasks. This was due to the enlargement of pupil size in those with light coloured iris when the black background was used. Therefore, tasks with white background was used later in the study whenever the eye tracker was having difficulties tracking the eyes with the black background.

The study demonstrated that, using the set-up described in Chapter 3 and the new calibration technique described in Chapter 4, EMR is feasible in young children with nystagmus, and also with special needs (DS). Recording was quite successful; out of a total of 85 children, useable data were obtained from 47. Not unexpectedly, success rates were higher among typically developing children (29 out 37) than among children with Down's syndrome (20 out of 40).

8.4 Retrospective calibration of eye movement recording in children

It is well known that pre-calibrating EMR in nystagmats can be a challenge due to the constant oscillation of the eyes. A breakthrough was achieved for analysis of eye movement data by the development and validation of a new method of calibrating horizontal and vertical EMR in nystagmats using smooth pursuit eye movement data (Chapter 5). The non-nystagmus eye movement data calibrated using this method produced similar data to the pre-calibrated data. When applied to un-calibrated nystagmus data, the retrospective calibration was also able to produce reliable calibrated data shown by fast phase amplitude and durations that follow the saccadic main sequence. This technique of calibration therefore can be applied to calibrate both nystagmus and non-nystagmus EMR data in children.

8.5 Previous investigations on diagnosis

Letters were sent to ophthalmologists of the participants to obtain information on the diagnosis and investigation methods of nystagmus (Chapter 6). In five children with DSN diagnosed with INS, the ophthalmologist reported the associated condition as

'Down's syndrome'. However, thorough follow up investigation of nystagmus was performed on only one child with DSN as compared to all three children in the TN group. This may be due to the fact that children with DS have not been reported to have any underlying cause of nystagmus. Therefore, further investigation is not deemed warranted. However, it can be argued that there is a difference in the case of children with DS that not all them have nystagmus. Therefore, there is remains, however unlikely, the possibility that the nystagmus is arising from a different reason not related to the DS. In light of my findings, the nystagmus associated with DS should be investigated in the same way as those without this condition. Ideally, this would involve performing at least an oculomotor assessment involving eye movement recordings, to ascertain that the nystagmus involves an accelerating waveform, and that it has the characteristics of IN.

8.6 Nystagmus characteristics in children with and without nystagmus

This study found that, generally, the characteristics of the nystagmus waveform of children did not differ from that of typically developing children with nystagmus (Chapter 6). Binocular VA of children with DSN also did not differ from typically developing children TN. This implies that nystagmus affects the VA of both groups of children in the same way. Perhaps it is surprising, therefore, that so few parents seem to have been made aware at hospital visits of the poor vision of their child with DSN, or that so few children were referred to the local VI service (see section 1.1)

Findings from the EMR data showed that the characteristics of the nystagmus waveform and VA of children with DSN cannot easily be distinguished from that of the TN group. This implies that nystagmus affects the VA of both groups of children in the same way. But of course, the causative relationship between nystagmus and VA is yet to be determined. EMR data showed the INS waveform types of both groups of children were variable when characterized using the 12 classical waveform (Dell'Osso and Daroff 1975), although children in the TN group showed a pattern where

nystagmus was more likely to be of pendular type in the younger children and jerk in the older children. This pattern was not seen in the DSN group of children. When characterized using the adaptationist method (Harris, Waddington and Erichsen 2012), type 1 nystagmus was the most common type of INS seen in both groups of children. This was also found in adults with IN as reported by Harris, Waddington and Erichsen (2012). FMNS-like waveform was only seen in 3 children with DSN and none in the TN group. These findings suggest that nystagmus in children with DSN and the visual acuity of both groups of children appear to be similarly affected.

8.7 Effect of nystagmus on fixation and smooth pursuit in children with and without DS

This experiment was conducted to investigate the eye movement performance of children with nystagmus with and without DSN, using a two-dimensional analysis (Chapter 7). To date, this method of analysing eye movement performance in nystagmus has only been applied to adults with IN. The two-dimensional analysis allows simultaneous assessment of eye movement performance horizontally and vertically. The results, which are expressed in terms of accuracy and precision, provide information on how well the children are able to match the target velocity and also how well they regulate their eye velocities when performing the eye movement tasks. This is important as retinal slip velocities may occur on both axes. I first examined the eye movement performance during fixation. The findings showed that both groups of children with nystagmus had poorer accuracy and precision than children without nystagmus. However, there was no statistically significant difference between the two groups with nystagmus for both accuracy and precision. I also discovered that there is a negative relationship between accuracy and nystagmus intensity in typically developing children with nystagmus. Increased nystagmus intensity corresponds to decreased accuracy during fixation. In children with DSN, however no significant correlation was found

I then assessed the children's eye movements during smooth pursuit. Similarly, there was no significant difference in gain, accuracy and precision between children in the DSN and TN group. However, there was a significant difference in gain and precision between children in the TN group and children in the DS and T group while children with DSN did not differ significantly from either group of children with no nystagmus. In terms of accuracy, a significant difference was seen only between children In the TN and T group. The fact that there was no significant difference in any of the eye movement performance between children with nystagmus with and without DS further suggests eye movement performance is similarly affected by nystagmus.

8.8 Limitations of the study

The biggest limitation of this study was the number of participants in both groups of children with DSN and TN. Although I had a large number of children joining the study (85 children), good quality EMR data was obtained from 51 (60%) children. Due to this, I had to pool the children with INS and FMNS-like waveform together causing the mean of the data to shift as FMNS-like waveforms are of low amplitude and intensity under binocular viewing. The results therefore showed that the characteristics of eye movement in this group of children were not significantly different statistically to that of children with no nystagmus with and without DS. A larger sample size would enable us to separate the children with different type of nystagmus into different groups and therefore allow a more comparable analysis. Since the number of children in both groups of children with nystagmus was small, I was also unable to investigate whether there was a change in the nystagmus waveform characteristics and eye movement performance with age. Nevertheless, the findings in Chapters 6 and 7 were able to provide an insight to the characteristics of nystagmus in children with DSN and the impact it has on their eye movement performance. I was not able to show that the nystagmus in children with DSN and TN had any obvious differences qualitatively (waveform) or statistically, which was the main aim of the study.

Another limitation of the study was the calibration of the EMR data. In this study, horizontal pursuit data was used to calibrate both horizontal and vertical EMR data. This resulted in the eye position data to be shifted to the left or right, depending on the SP ramp used for the calibration. To obtain the actual eye positions, both rightward and leftward ramps would need to be used. Unfortunately, this was not possible as some of the children in the study only had good clean data for only one of the ramps. As a consequence, our study was restricted to the analysis of velocity data. Nevertheless, the results from this study using velocity data were sufficient to answer our question of how nystagmus affects the eye movement performance of children with nystagmus with and without DS.

Finally, the eye movement performance during pursuit was limited to horizontal target movement. I have established that children in general have short attention span. In this study, the children had to undergo a series of optometric tests prior to the EMR. When it was time to do the eye movement recording, fatigue would have kicked in. Therefore, in the interest of maintaining the children's cooperation, the number of eye movement tasks were reduced.

8.9 Future work

8.9.1 How the eye movement performance during fixation and smooth pursuit metrics evolve as a function of age in children with nystagmus

Initially, I wanted to look at the development of eye movement performance during fixation and smooth pursuit in children with nystagmus, with and without DS. However, due to the limitations of low sample size, it was not possible to look at the changes of eye movement performance with age. Previous studies of eye movement performance on typically developing children with no nystagmus have shown that smooth pursuit performance improves with age and matures between 7 years old (Ingster-Moati et al. 2009; Vinuela-Navarro 2015). Visual fixation control and stability have also been shown to improve with age in this group of children (Luna et al 2008;

Luna & Velanova 2011). Very little is known of the development of eye movement performance in children with nystagmus, with and without DS. Understanding the changes in eye movement performance (if any) in these groups of children may help to improve the management of these children such as in school and daily activities.

8.9.2 Pursuit performance with different target frequencies and direction

Due to the limitations of attention and cooperation, I only investigated the performance during horizontal pursuit at one velocity and amplitude. However, it has been shown that different target frequencies (acquired by combining different pursuit amplitudes and target velocities) can affect the smooth pursuit performance in adults with IN (McIlreavy 2016) Since objects in the real world move at a variety of frequencies and direction, it would be beneficial to investigate the smooth pursuit performance of children with nystagmus with and without DS at different target frequencies and direction.

8.9.3 Dynamic visual acuity in children with nystagmus with and without DS

The results of smooth pursuit performance in this study highlight how VA may overestimate visual function in those with nystagmus. In clinic, the children are given time (i.e. many foveations) as necessary to look at stationary targets. However, objects in the real world are not always stationary. Hence, it will be difficult for children with nystagmus to get the maximum resolution part of the retina, i.e. fovea, onto the target. Thus, static VA may overestimate the real-world VA. Further research might explore dynamic VA in children with nystagmus to determine their actual visual function.

8.9.4 Effectiveness of correcting refractive errors in children with nystagmus with and without DS

The findings from our retrospective study in Chapter 2 and cross-sectional study in Chapter 6 showed that seventeen (65.4%) children with DSN presented significant refractive error, which was not significantly different from typically developing children with nystagmus. Correction of significant refractive errors often results in improvement of visual acuity in the typical population (Stewart et al. 2004; Cotter et al. 2007). Therefore, it is an ethical responsibility of the healthcare system to correct any significant refractive error. Prescription of spectacle correction has been suggested as an intervention for nystagmus. However, high prescription spectacle causes magnification or minification of the image, and can limit the field of view. However, spectacles can hinder the use of a null point that is eccentric. Further research should be undertaken to explore whether prescriptions of spectacles are helpful or a hindrance to children with nystagmus both with and without DS.

8.10 Summary

The current study has not identified any obvious differences in the nystagmus waveform types between children with DSN and typically developing children, and certainly there was no significant difference found. Moreover, the degree of visual impairment as measured by VA was similar in both groups of children. There was also no statistical difference in the accuracy or precision of eye movements during fixation and smooth pursuit between the two groups of children with nystagmus, further suggesting that nystagmus has a similar impact on both groups of children. Despite the relatively small numbers in the study, it is clear that nystagmus in typical children is much more likely to be investigated thoroughly than is nystagmus in children who also have DS. It is understandable that performing tests such as MRI or VEP may be unnecessary, as underlying conditions generally have not been reported to be associated with those with DSN, but simply associating the nystagmus with the DS may cause the impact of nystagmus on this group of children to be overlooked. The findings

from this study argue that, at the least, any investigation of nystagmus should be applied equally in all children with nystagmus, ideally by oculomotor assessment with eye movement recording. The diagnosis of the nystagmus type as well as a measurement of the visual status of these children will enable them to get access to the visual support services that they require.

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APPENDIX

Appendix A: Amendment approval for school ethics for pilot studies involving adults

SCHOOL RESEARCH ETHICS AUDIT COMMITTEE

CARDIFF UNIVERSITY
PRIFYSGOL CAERDYDD

Project Number: 1325

Amendment No. 2

Project title: Using theories of how the eyes are controlled to understand why people perceive the world as stable

Lead Investigator(s): Lee McIlreavy

Date: 13/07/2015 Project end date: 2016

With reference to the above application, I am pleased to confirm that the request to amend the above ethics application has been granted.

These amendments include:

1. A change in the title of project number 1325 from 'Models of oculomotor control as a means of understanding oscillopsia' to "Using theories of how the eyes are controlled to understand why people perceive the world as stable". It should be noted that all previously approved ethical materails under project 1325 use the latter project title, not the former. This was at the request of the school research ethics committee that the title be changed so that it could be understood by the lay public.

2. The addition of a new researcher, Asma Ahida Binti Ahmad Zaidi.

Please inform the School Research Ethics Audit Committee immediately of any changes to the protocol, changes to personnel involved, or of any unforeseen circumstances arising from the study.

Please note the data retention periods specified by the University

- For non-funded non-clinical research, data shall be retained for no less than 5 years, or 2 years post-publication
- Undergraduate project data shall be retained at least until the end of the University appeals process

Signed:

Appendix B: Amendment approval for NHS ethics for main studies involving children with DS and typically developing children with nystagmus

Ymchwil Iechyd a Gofal Cymru
Health and Care Research Wales

Gwasanaeth Moeseg Ymchwil
Research Ethics Service

Ariennir gan **Lywodraeth Cymru**
Funded by **Welsh Government**

Wales REC 3
Sixth Floor, Churchill House
17 Churchill Way
Cardiff CF10 2TW

Telephone : 029 2037 6829
Fax : 029 2037 6824
E-mail : corinne.scott@wales.nhs.uk
Website : www.hra.nhs.uk

28 August 2015

Dr J Margaret Woodhouse
Senior Lecturer
Cardiff University
School of Optometry and Vision Science
Cardiff University,
Maindy Road
Cardiff CF24 4LU

Dear Dr Woodhouse

Study title: **Visual Development and Visual Defects in Children with Down's Syndrome**
REC reference: **08/MRE09/46**
Protocol number: **SPON 536-08**
Amendment number: **3**
Amendment date: **17 July 2015**
IRAS project ID: **3389**

The above amendment was reviewed [at the meeting of the Sub-Committee held on 28 August 2015.

The members of the Committee taking part in the review gave a favourable ethical opinion of the amendment on the basis described in the notice of amendment form and supporting documentation.

Approved documents
The documents reviewed and approved at the meeting were:

Document	Version	Date
Notice of Substantial Amendment (non-CTIMP)	3	17 July 2015
Other [Researcher CV]	Asma Binti Ahmad Zahidi	07 July 2015
Participant information sheet (PIS) [Parent/guardian information sheet and consent form (control children)]	3.1 (July 2015)	
Participant information sheet (PIS) [Parent/guardian information sheet and consent form (children with Down's syndrome)]	3 (July 2015)	
Research protocol or project proposal [Parent/guardian information sheet and consent form (children with Down's syndrome)]	3, July 2015 (track changes)	

Membership of the Committee
The members of the Committee who took part in the review are listed on the attached sheet.

All investigators and research collaborators in the NHS should notify the R&D office for the relevant NHS care organisation of this amendment and check whether it affects R&D approval of the research.

Appendix C: Amendment approval for school ethics for pilot studies involving typically developing children

School of Optometry and Vision Sciences
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SCHOOL RESEARCH ETHICS AUDIT COMMITTEE

Project Number: 1321

Amendment No. 5

Project title: The Assessment of tracking difficulties in children

Lead Investigator(s): Dr M Woodhouse, Flor Vinuela Navarro

Date: 15/10/2015 **Project expiry date: 24th July 2018**

With reference to the above application, I am pleased to confirm that the request to amend the above ethics application has been granted.

These amendments include:

1) Extend the project to July 2018
2) Study extended to include 30 infants and pre-school children and 30 – 50 individuals aged over 18 years.
3) Additional investigators added (Asma Ahida Binti Ahmad Zahidi & Miss Alicja Sidorowicz)

Please inform the School Research Ethics Audit Committee immediately of any changes to the protocol, changes to personnel involved, or of any unforeseen circumstances arising from the study.

Please note the data retention periods specified by the University

- For non-funded non-clinical research, data shall be retained for no less than 5 years, or 2 years post-publication
- Undergraduate project data shall be retained at least until the end of the University appeals process

Signed:

Approval form 2014_0809

Appendix D: Study information sheet and consent form for adults

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PARTICIPANT STUDY INFORMATION SHEET

Using theories of how the eyes are controlled to understand why people perceive the world as stable

Approval No: 1325
Version: 1.2N
Date: 26/06/15

What is this study about?

Nystagmus is a word used to describe a constant to-and-fro movement of the eyes. The purpose of this study is to find out how nystagmus will affect the ability to see moving and stationary objects.

Who is carrying out this study?

I (Ms Asma Zahidi) am an optometrist and a PhD student at the School of Optometry and Vision Sciences at Cardiff University. I will be carrying out this study as part of my PhD thesis, under supervision by Professor Jonathan Erichsen (School of Optometry and Vision Sciences). Contact details for each person are given at the end of this information sheet.

Why have I been invited to take part?

I need to gain as much information as possible about the eye movements of people with nystagmus so that a comparison can be made with people who have normal vision (i.e. without nystagmus). Therefore, your participation is very valuable. You must be aged 18 years or older to take part in this study.

Do I have to take part?

No, your participation in this study is entirely voluntary. Your decision about whether or not to participate in this study will have no consequences and it will not affect your rights or access to services or benefits at the School of Optometry and Vision Science. You can withdraw from the study at any time, without giving a reason.

What will happen to me if I take part?
If you agree to participate, you will be invited to attend the School of Optometry and Vision Sciences building (Maindy Road).

This study will involve a single visit. During this visit you may take part in a number of experiments, each of which last approximately 20-30 minutes. You may choose to take part in as many or as few experiments as you wish. Breaks will be given between each experiment to prevent fatigue. When you visit I will measure your ability to see increasingly smaller letters, measure your ability to see faint letters, and I will determine the alignment of your eyes. I will also ask some questions about the health of your eyes and your general health.

In all of the experiments you will be asked to view simple shapes or patterns (e.g. dots or crosses) on a large projector screen. The shapes/patterns will either be stationary or moving. You will be asked to look at or follow a particular shape/pattern You will be provided with instructions before you begin the experiment. In addition I will record where you are looking using a non-contact, remote eye tracking system.

Do I need to do anything special to take part?
No.

What are the possible benefits of taking part?
Although no immediate benefit is likely to arise as a result your participation in this study, the information obtained will contribute to our understanding of how people with nystagmus see moving and stationary objects.

Are there any possible risks from taking part?
No, there are no foreseeable risks involved if you participate in this study. However if you feel uncomfortable at any point during the study, the experiment can be stopped and no further participation is necessary.

Will my results remain confidential?
Your study data and confidential information will be kept for 10 years. We will need to keep your information for this time because further analysis and review of your data may be necessary. Also, if the results are to be published in a journal, it will help answer any future queries or disputes other scientists may have about the results. After 10 years, all confidential information that we hold about you will be destroyed (i.e shredded) by the Security Services at Cardiff University, and any study

data (i.e. records about where your eyes were looking during an experiment) will be erased from computers using specialist software designed for this purpose. The procedures within the School of Optometry and Vision Sciences and the School of Psychology are compliant with the Data Protection Act 1998.

What will happen to the results of this study?
I aim to present the results of this study at conferences and to publish the results in scientific journals and as part of my PhD thesis. Results and findings from the study will be summarized and will be published on the Nystagmus Network website (http://www.nystagmusnet.org/cms/). It will not be possible for someone to identify you in any conference materials, scientific journals or from the PhD thesis. All personal information that is collected about you during the course of this study will be kept strictly confidential and stored in locked file cabinets. A unique participant code will be used on all of your experimental data forms and electronic data files so it will not be possible for others to identify you. The unique identifier codes will be known only to the three investigators in the research group, and will be recorded in a file retained in a locked cabinet.

Who has reviewed the study?
This study has been reviewed and ethically approved by the Research Ethics Committee at the School of Optometry and Vision Sciences, Cardiff University.

How do I withdraw from the study?
If you would like to withdraw from the study, you can do so by contacting me (Ms Asma Zahidi) using the details provided at the end of this information sheet. If you withdraw from the study I will erase your study data (i.e. records about where your eyes were looking during an experiment) and any personal information you provided will be destroyed (i.e. shredded) by the Security Services at Cardiff University.

What if I have any questions or if I have a problem?
If you have any questions or problems, please contact one of the investigators below:

Name	Telephone	Email
Ms Asma Zahidi	029 208 70556	BintiAhmadZahidiAA@cardiff.ac.uk
Prof Jonathan Erichsen	029 208 75656	ErichsenJT@cardiff.ac.uk
Dr Lee McIlreavy	026 208 70134	mcilreavy@cardiff.ac.uk

Alternatively, if you would like to make a complaint about any part of the study or any investigator(s) named above, you can do so by contacting the secretary for Research Ethics Commitee at the School of Optometry and Vision Sciences:

Name	Telephone	Email
Mrs Leanne Morrish	029 208 79048	JonesLE8@cardiff.ac.uk

Thank you for taking time to read this information.

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STUDY CONSENT FORM

Using theories of how the eyes are controlled to understand why people perceive the world as stable

Approval No: 1325
Version: 1.2N
Date: 26/06/2015

Name of Researchers: Ms Asma Zahidi, Professor Jonathan T. Erichsen, Dr Lee McIlreavy

Please initial box

1 I confirm that I have read and understand the Participant Information Sheet (Version: 1.2N Date: 26/06/15) for the above study and have had the opportunity to ask questions. ☐

2 I understand that my participation is voluntary and that I am free to withdraw at any time without giving any reason and without any consequences. ☐

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

Name of Participant	Date	Signature

Name of Person taking consent (if different from researcher)	Date	Signature

Researcher	Date	Signature

Appendix E: Study information sheet and consent form for children with DS and typically developing children with nystagmus

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PARTICIPANT INFORMATION SHEET

Visual development and visual deficits in children with Down's syndrome

We would like to invite you and your child to take part in our study. Before you decide, you need to understand why the research is being done and what it would involve for your child. Please take time to read the following information carefully.

Who are we?
At the Down's Syndrome Vision Research Unit, we have been studying visual development in children with Down's syndrome since 1992. Children with Down's syndrome are at much greater risk of eye and vision disorders than are typically developing children. For example, older children with Down's syndrome have eyes which are a different shape to typical eyes.

Why are we asking you to enrol your child in the study?
Children with Down's syndrome are at much greater risk of eye and vision disorders than are typically developing children. Even when children wear glasses to correct long or short-sight, or even if they do not need glasses, children with Down's syndrome may have some visual difficulties. It is, therefore, very important that we understand the ways in which children's eyes develop and how we can best help them make the most of their vision.

What will we do?

The study will involve recording how your child's eyes move and how they focus at different distances while he/she is performing different visual tasks such as following moving objects, looking at a cartoon that appears in different screen location or scan a picture. Your child simply needs to keep still for a very short time and perform the different visual tasks presented.

To record the how your child's eyes move and focus, we will use a power refractor and/or an eye tracker. Although these instruments are very modern and sophisticated, all measurements are non-invasive, and we do not use drops.

We would also like to record the usual clinical measures we make during a normal eye examination, of spectacle prescription and detail vision, as well as your child's age.

What are the disadvantages and risks of my child taking part?
There are no potential risks in taking part. However, this study is not suitable for individuals with epilepsy due to health and safety issues that arise from the use of computer screens. It is not anticipated that participation will cause distress in any way.

Will my child's information be confidential?
The information about you and your child remains completely confidential. Ms Ahmad Zahidi and Miss Vinuela-Navarro will be using the results for their PhD and postdoctoral studies, respectively. When they write their dissertation/reports, and when we publish research results (in journals or in talks etc.) we do not identify your child in any way. We do like to use photographs of the children as often as possible for teaching purposes, such as lectures and posters, but we always ask for your permission first, and of course, send you a copy of the photograph. We may want to write to your child's consultants to obtain more information about your child's eyes and general health. Are you happy for us to do so?

Will I know the results of the research?
If you indicate on the consent form that you would like to hear about the results, we will keep your contact details, and will send a report to you in due course.

Do I have to enrol my child?
Children who join our study are extremely valuable to us and we appreciate all of the effort that parents put in to take part. Children who cannot co-operate are just as valuable, because measuring the success rate of the instruments is important information. But joining the study is voluntary, and you have the right to refuse. In any case, we respect your decision and it will not affect the standards of eye care your child will get in our clinic.

What happens if I want to withdraw my child from the study?
You are free to withdraw at any time, without giving a reason. However, any published results that included your child's data will be impossible to modify or discard. Nonetheless, if you decide to withdraw your child, we promise not to use his/her past and future results in any further studies that take place after the date on which we are informed of your decision.

If you are happy for your child to join the study, please sign the form overleaf

J. Margaret Woodhouse Flors Vinuela-Navarro Asma Binti Ahmad Zahidi

Tel: +44 (0)29 2087 6522

Email: woodhouse@cf.ac.uk
http://www.cardiff.ac.uk/optom/DownsSyndromeGroup/Home.html

The work of the Down's Syndrome Vision Research Unit has been funded over the years by:
The Down's Syndrome Association, Mencap with the Community Fund, Mencap City Foundation, PPP Foundation, National Eye Research Centre, Welsh Assembly Government

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CONSENT FORM

Visual development and visual deficits in children with Down's syndrome

Name of Researchers: Dr J. Margaret Woodhouse, Miss Valldeflors Vinuela Navarro, Ms Asma Asma Binti Ahmad Zahidi

		Initials
1	I confirm that I have read and understand the Participant Information Sheet (Main study Version 3. Date July 2015) for the above study. I have had the opportunity to consider the information, ask questions and have had these answered satisfactorily.	☐
2	I understand that my participation is voluntary and that I am free to withdraw at any time without giving any reason, without my medical care or legal rights being affected.	☐
3	I agree to take part in the above study.	☐
4	I agree to allow the researchers to write to my child's consultant to obtain information on his/her eyes and general health	☐
5	I would like to receive information on the results of this study Name: _____ Address: _____ _____ Email: _____	☐

Child's name	Date of birth

Name of Parent/guardian/legal tutor	Date	Signature

Researcher	Date	Signature

Appendix F: Study information sheet and consent form for typically developing children with no nystagmus

School of Optometry and Vision Sciences
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PARTICIPANT INFORMATION SHEET

Title: The assessment of tracking difficulties in children

Principle investigators Miss. Valldeflors Viñuela Navarro, Dr. Margaret Woodhouse, Dr. Jonathan Erichsen and Mrs. Cathy Williams, Ms. Asma Zahidi

Children are invited to take part in a research study. Before consent is given to take part, it is important that you understand why the research is being done and what it will involve. Please take time to read the information and talk to others about it if you wish.

What is the purpose of the study?

The main purpose of this study is to establish normative values for tracking eye movements in infants and young children. Tracking eye movements are the eye movements we perform when we follow a moving object, for example when looking a moving car, a football, etc. The study will provide a better understanding of these particular eye movements in infants and young children and improved guidelines for optometrists and their clinical examination.

What will happen to my child if he/she take part?

Initially, we will take some measurements of the child's eyes to determine how well he/she can see (with his/her specs prescription if any). We will also measure how the eyes move and work together using standard optometric methods. Following this, we will record the child's eye movements while the child performs one or more visual tasks. For example, tracking a point or a picture that moves across the screen. Please, note that this is not a full eye examination and that the child should visit the optometrist when his/her next test is due.

What are the possible risks of taking part?

All of the instruments which will be used in this research are child-friendly and are currently used in different studies. The instruments used establish eye orientation and position by measuring the reflection of light from the eye. There are no potential risks in taking part.

How long will it last?

The study visit will last no more than 15 minutes. However, the child may be invited to return if additional information is required (due to excessive blink or head movements, inattention, etc.).

What is the benefit of taking part?

Participating in this study may not benefit you and/or the child directly but we will learn more about eye movement abnormalities in children and their association with learning difficulties. This may help us to detect and diagnose children with eye movement abnormalities that may present a possible risk to learning.

Will my taking part be confidential?

All data obtained will be stored on a computer and will not be made available to any third party, and no personal information will be stored. Any results published will be anonymous. A copy of the data held on computer about you is available on request in accordance with the Data Protection Act.

Will I have information about the results of the study?

If you are interested in our study and would like to know more about it and the results obtained we are very happy to post you a final short report. This report will be sent to participants on request. If you want to receive the report at the final of the study tick the box below and write your contact details.

□ *Yes, I would like to receive a report with more information about the project and the results obtained at the end of the study*

Name and contact details:

_____

_____

_____

_____

Contact details

It is up to you and the child whether you take part and you are free to withdraw from the study at any time. If you decide to take part you can ask questions at any time. If you have any questions about this research, please contact:

Asma Ahida Ahmad Zahidi
Email: BintiAhmadZahidiAA@cardiff.ac.uk
School of Optometry and Vision Sciences, Maindy road. CF24 4HQ.

Or

Dr Margaret Woodhouse
E-mail: Woodhouse@cardiff.ac.uk
School of Optometry and Vision Sciences, Maindy road. CF24 4HQ.

School of Optometry and Vision Sciences
Ysgol Optometreg a Gwyddorau'r Golwg

Head of School *Pennaeth Yr Ysgol* Professor *Yr Athro* Marcela Votruba

College of Biomedical and Life Sciences
Cardiff University
Maindy Road
Cardiff
CF24 4HQ
Wales UK

Tel *Ffôn* +44(0)29 2087 4374
Fax *Ffacs* +44(0)29 2087 4859
http://www.cardiff.ac.uk/optom/

Prifysgol Caerdydd
Heol Maindy
Caerdydd
CF24 4HQ
Cymru, Y Deyrnas Gyfunol

CONSENT FORM

Assessment of tracking difficulties in children

Name of Researchers: Miss. Valldeflors Viñuela Navarro, Dr. Margaret Woodhouse, Prof. Jonathan Erichsen and Mrs. Cathy Williams, Ms. Asma Zahidi

1 I confirm that I have read and understand the Participant Information Sheet (Version 3 Date September 2015) for the above study. I have had the opportunity to consider the information, ask questions and have had these answered satisfactorily. ☐

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

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

4 I would like to receive information on the results of this study ☐
Name: _____
Address: _____
_____
Email: _____

Child's name	Date of birth	
Name of Parent/guardian/legal tutor	Date	Signature
Researcher	Date	Signature

Appendix G: Example of the letters sent to ophthalmologists

C9265922

Cardiff and Vale Univeristy Health Board
Ymddiriedolaeth GIG Caerdydd a'r Fro
University Hospital of Wales
Ysbyty Athrofaol Cymru

Eich cyf/Your ref
Ein cyf/Our ref
Welsh Health Telephone Network 1872
Direct Line/Llinell uniongyrchol

Heath Park
Cardiff CF14 4XW
Phone (029) 2074 7747
Minicom (029) 2074 3632

Parc Y Mynydd Bychan,
Caerdydd CF14 4XW
Ffôn (029) 2074 7747
Minicom (029) 2074 3632

CARDIFF EYE UNIT
Consultant - Mr Patrick Watts
Secretary - Tina McDonald
Direct Line: (Tel 02920 748583) (Fax 02920 742250)
Email : tina.mcdonald@wales.nhs.uk

Ophthalmologist
Eye Clinic
~~Prince Phillip Hospital~~,
~~Bryngwyn Mawr~~,
~~Dafen~~,
~~Llanelli~~,
~~Carmarthenshire~~,
~~SA14 8QF~~

2nd May 2018

Dear Sir / Madam,

My colleagues at the School of Optometry & Vision Sciences and I carrying out a research study into the characteristics of nystagmus in children. I am writing to ask you to confirm the diagnosis for:

Name: ~~Menna R. Hickman~~
DOB: ~~17/10/2011~~
Address: ~~2, Cern Padris, Llanelli SA15 2DF~~

I am attaching a copy of the study consent form in which the parent(s) agree to our contacting you. We would appreciate it if you could fill in the attached form and return it to my colleague at the address on the form.

Yours sincerely,

Patrick Watts MBBS, MS, FRCS, FRCOphth
Consultant Paediatric Ophthalmologist

Appendix H: Investigation and diagnosis of nystagmus form sent to ophthalmologists

Name:
DOB:
Address:

I confirm the diagnosis for the above patient of:

Infantile / congenital nystagmus:

Associated with any ocular conditions (please state): ☐

_____

Not associated with any other ocular conditions ☐

Latent nystagmus ☐

Unknown / unsure ☐

Which of the following investigations (if any) led to the diagnosis?

ERG ☐

VEP ☐

Eye tracking ☐

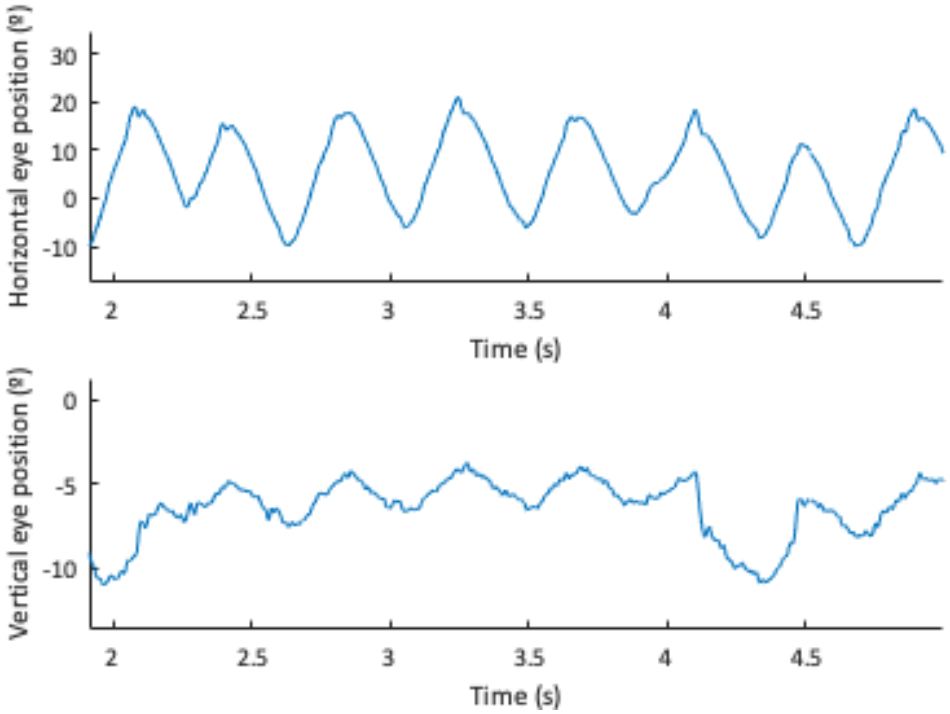
Orthoptic assessment ☐

Date of diagnosis: _____

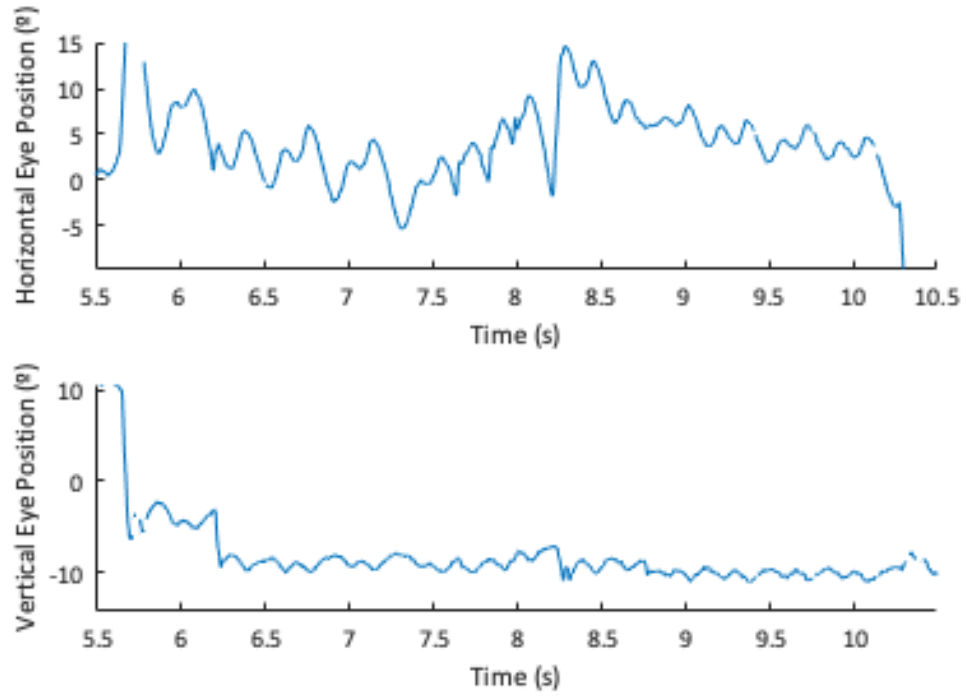
Please return to:
Asma Zahidi
c/o Patrick Watts
School of Optometry & Vision Sciences
Cardiff University
Maindy Road
CF24 4HQ

Appendix I: Horizontal and vertical eye trace of children in the DSN group

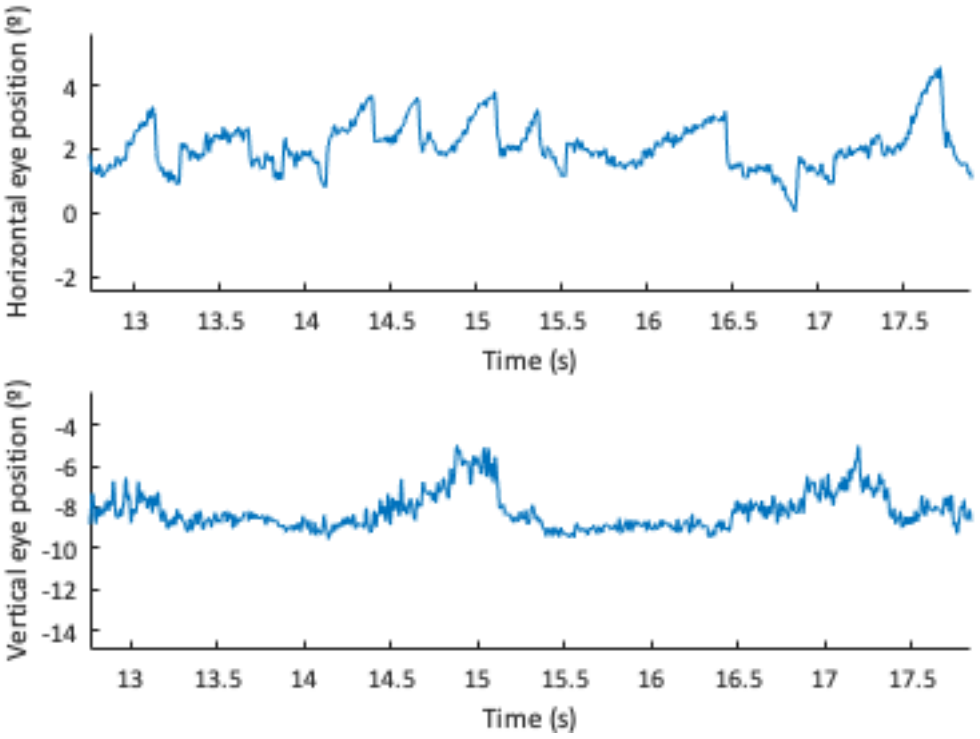
P15



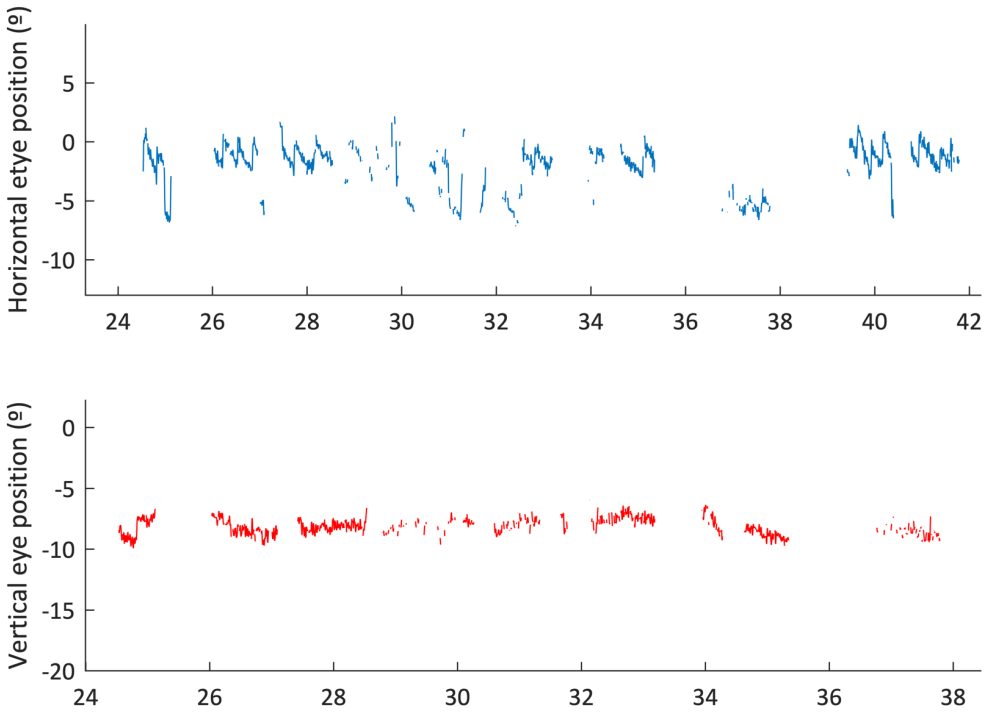
P17



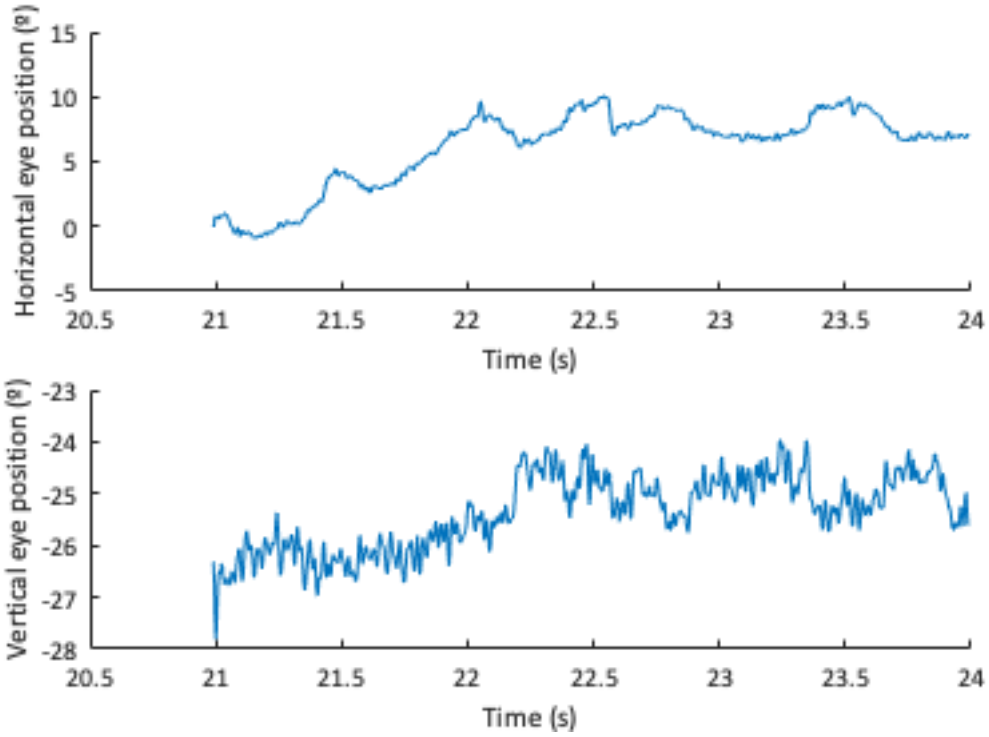
P22



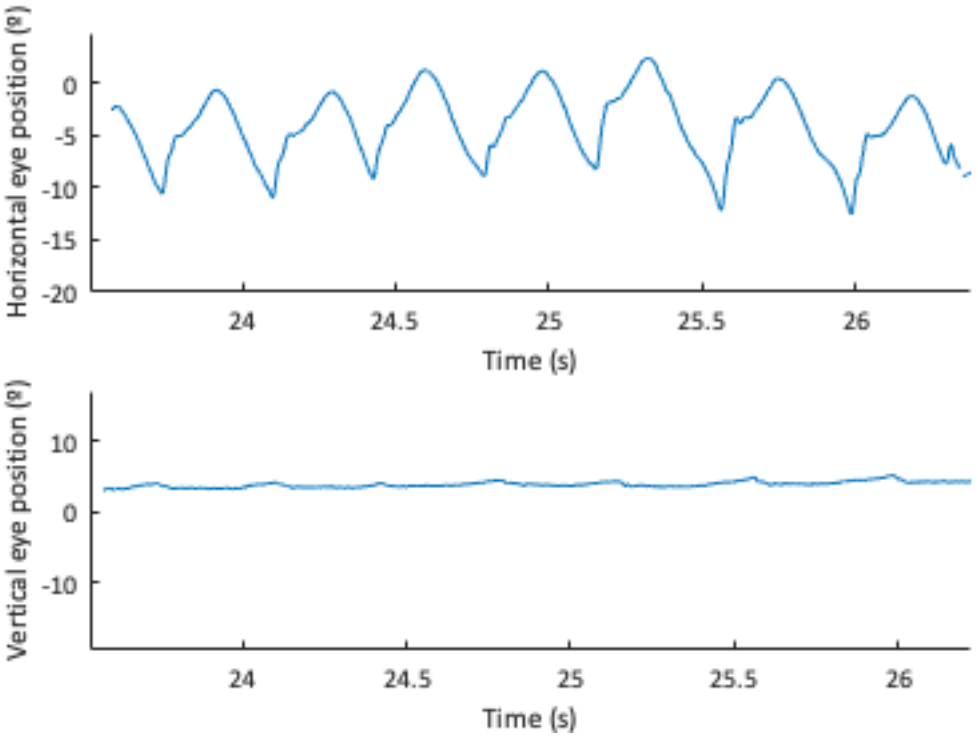
P34 FMNS (RE viewing)



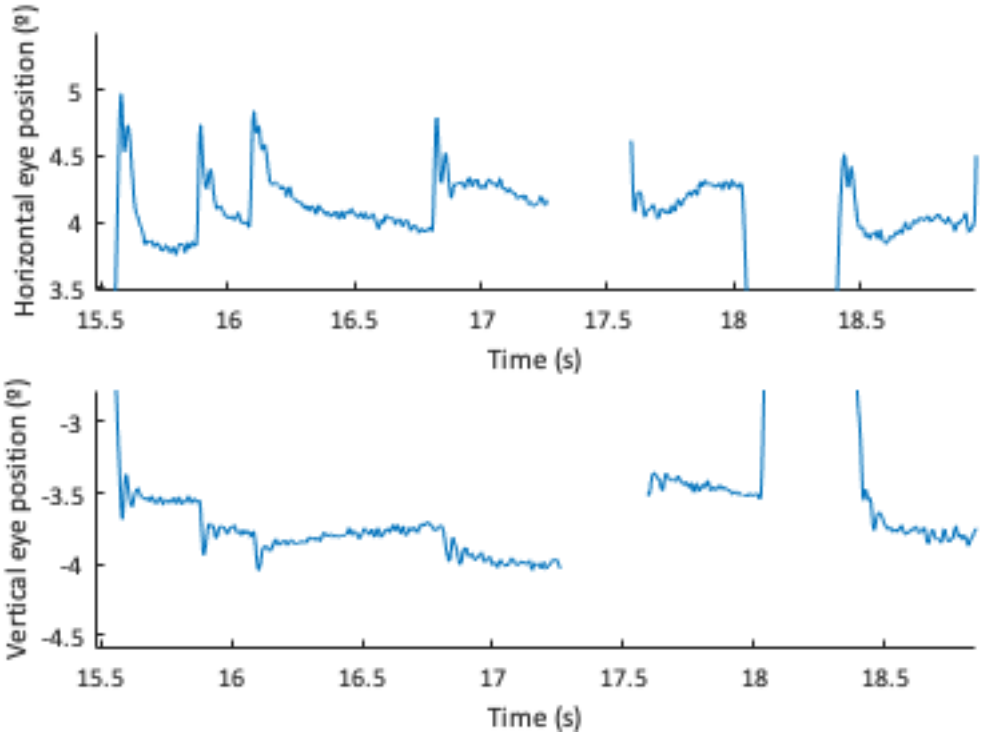
P67


Horizontal eye position (º)
15
10
5
0
-5
20.5
21
21.5
22
22.5
23
23.5
24
Time (s)
Vertical eye position (º)
-23
-24
-25
-26
-27
-28
20.5
21
21.5
22
22.5
23
23.5
24
Time (s)

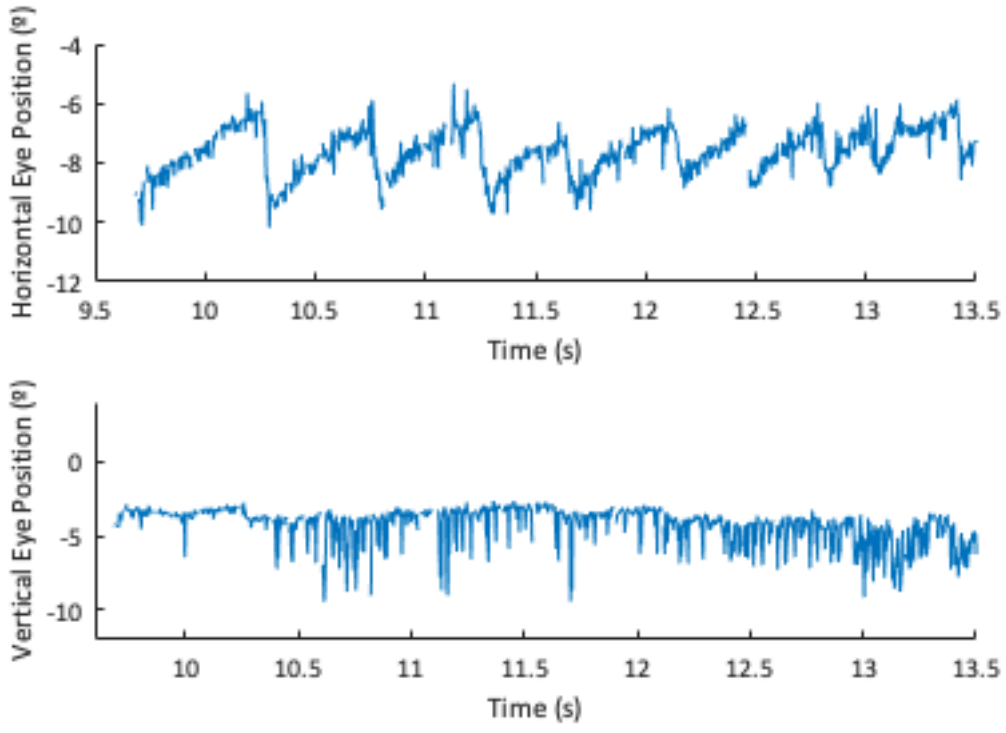
P69


Horizontal eye position (º)
0
-5
-10
-15
-20
24
24.5
25
25.5
26
Time (s)
Vertical eye position (º)
10
0
-10
24
24.5
25
25.5
26
Time (s)

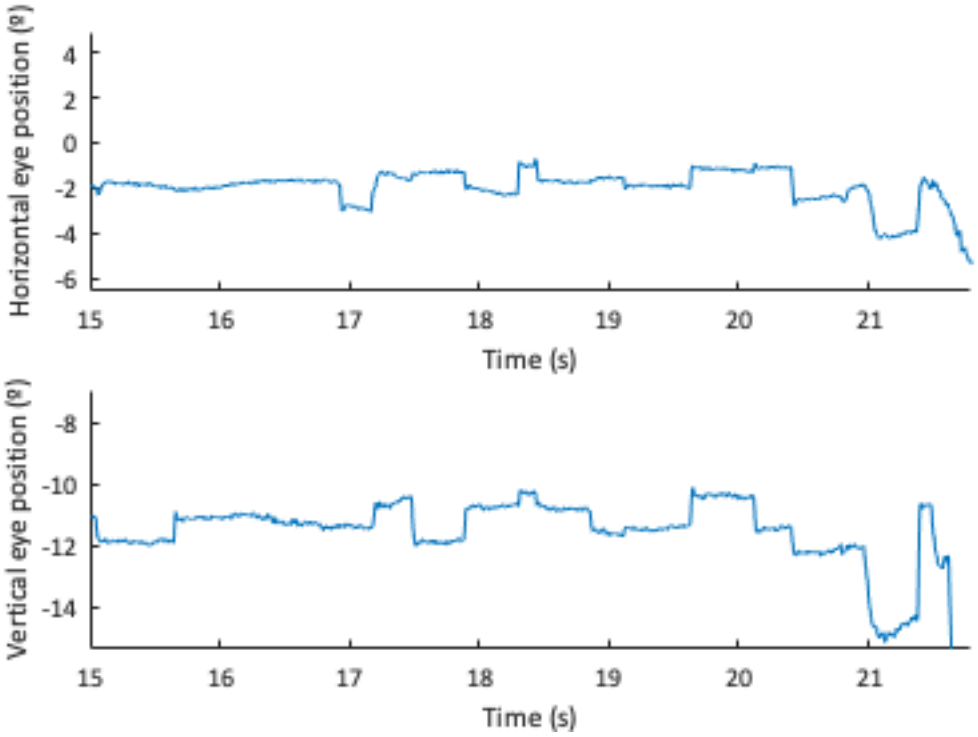
P72 - FMNS


Horizontal eye position (º)
5
4.5
4
3.5
15.5
16
16.5
17
17.5
18
18.5
Time (s)
Vertical eye position (º)
-3
-3.5
-4
-4.5
15.5
16
16.5
17
17.5
18
18.5
Time (s)

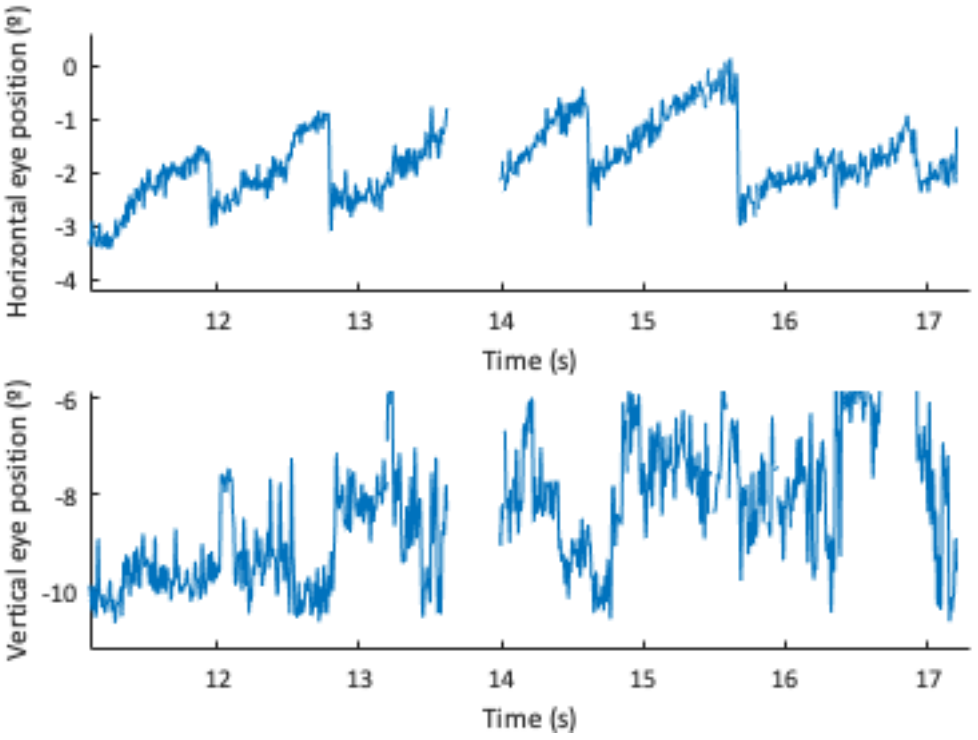
P76


Horizontal Eye Position (º)
-4
-6
-8
-10
-12
9.5
10
10.5
11
11.5
12
12.5
13
13.5
Time (s)
Vertical Eye Position (º)
0
-5
-10
10
10.5
11
11.5
12
12.5
13
13.5
Time (s)

P81 - FMNS

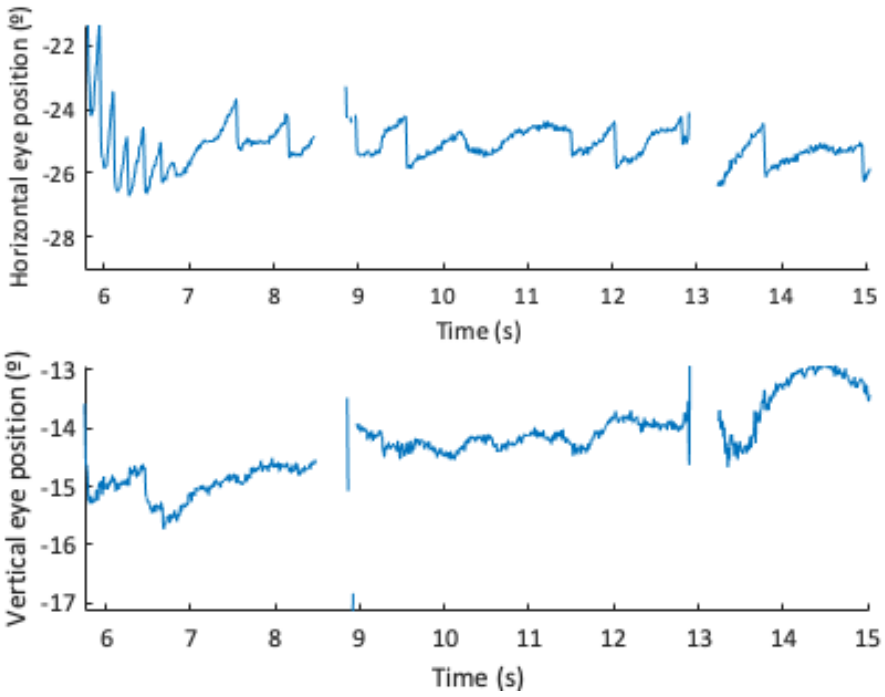

Horizontal eye position (º)
4
2
0
-2
-4
-6
15
16
17
18
19
20
21
Time (s)
Vertical eye position (º)
-8
-10
-12
-14
15
16
17
18
19
20
21
Time (s)

P82

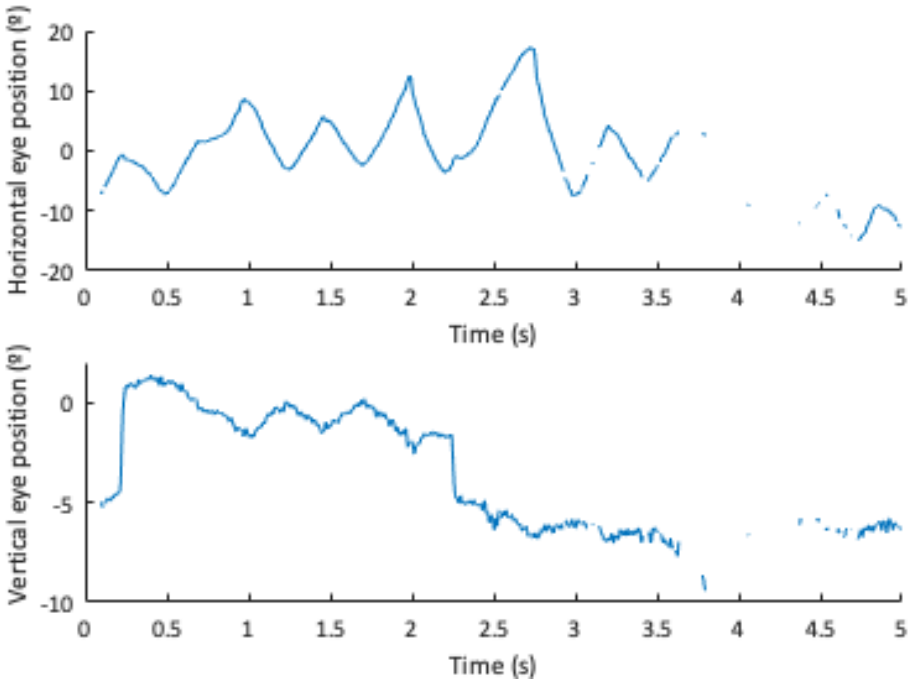

Horizontal eye position (º)
0
-1
-2
-3
-4
12
13
14
15
16
17
Time (s)
Vertical eye position (º)
-6
-8
-10
12
13
14
15
16
17
Time (s)

Appendix J: Horizontal and vertical eye trace of children in the TN group

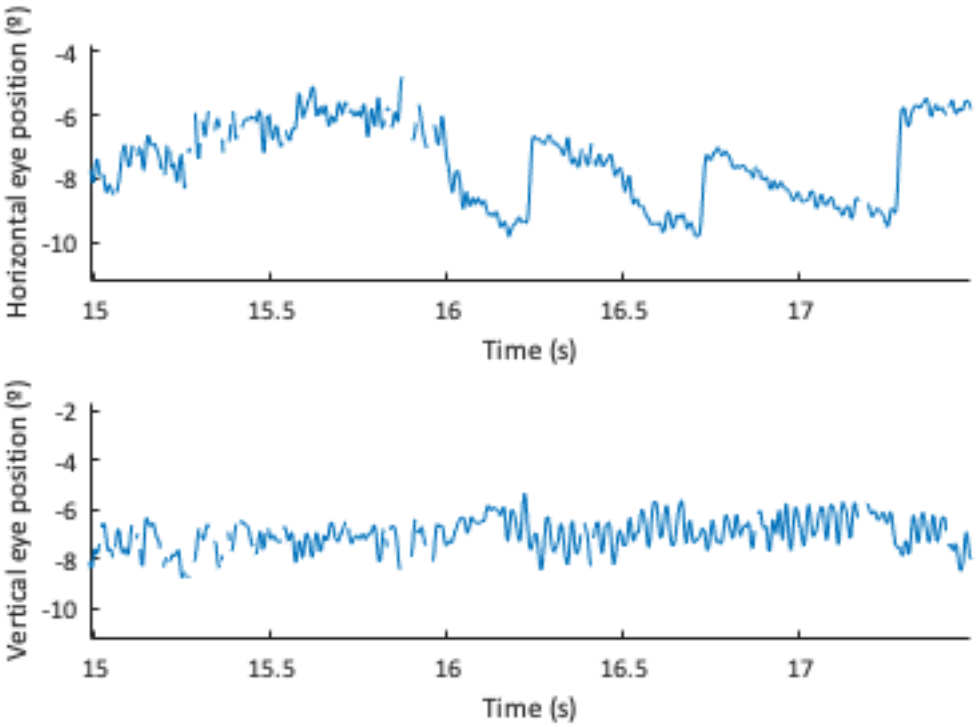
P04 – Left gaze



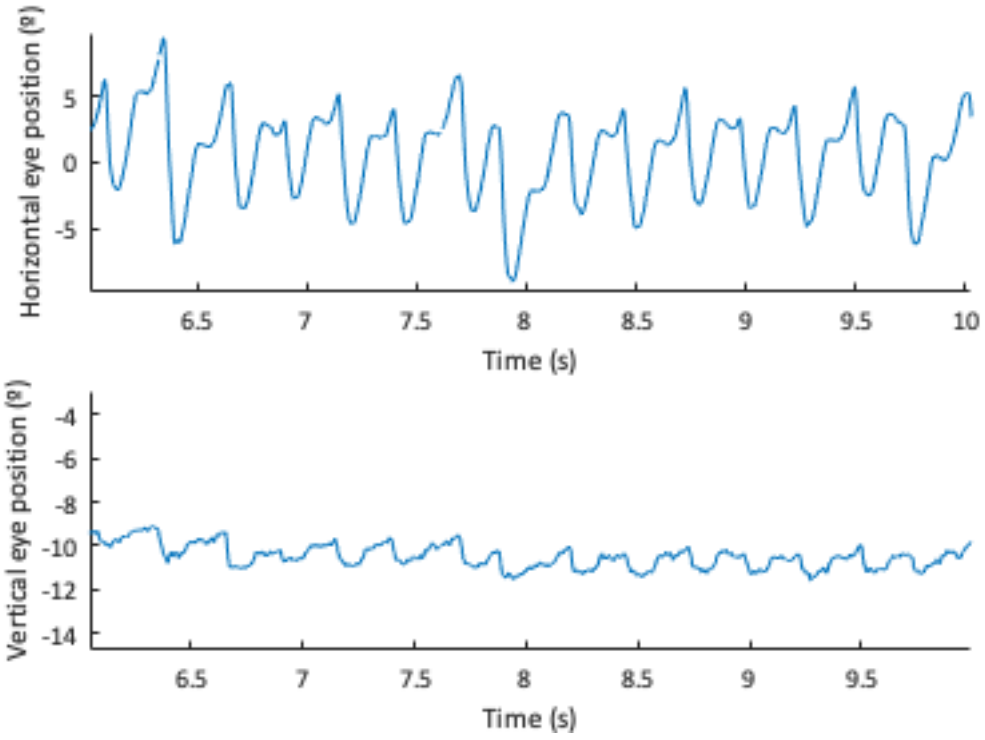
P14



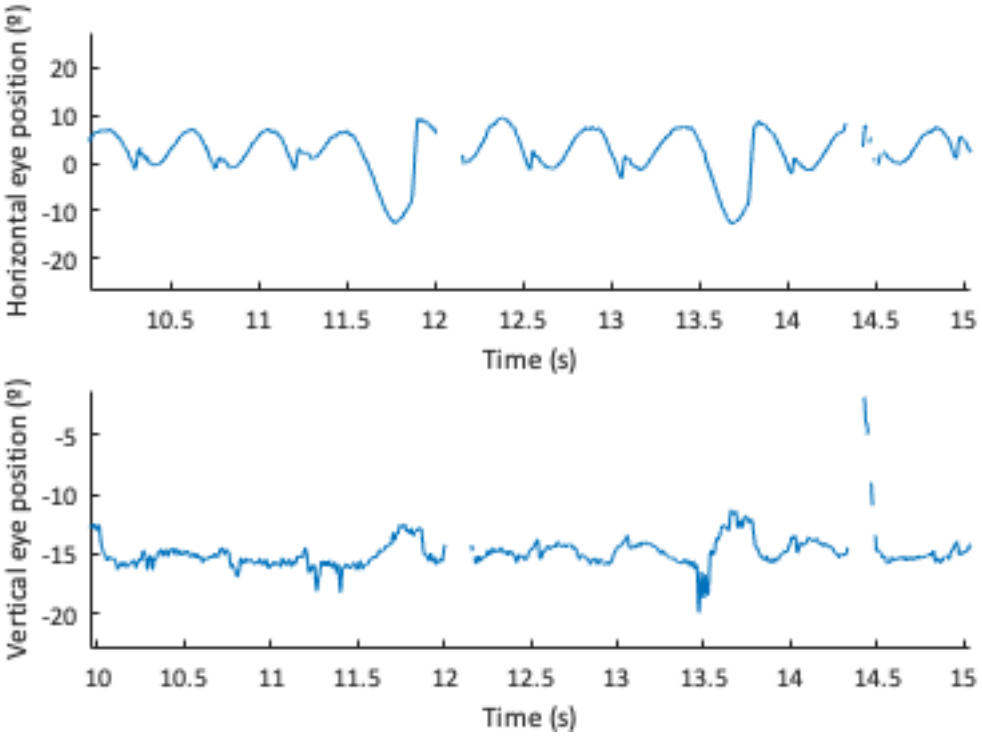
P32


Horizontal eye position (º)
-4
-6
-8
-10
15
15.5
16
16.5
17
Time (s)
Vertical eye position (º)
-2
-4
-6
-8
-10
15
15.5
16
16.5
17
Time (s)

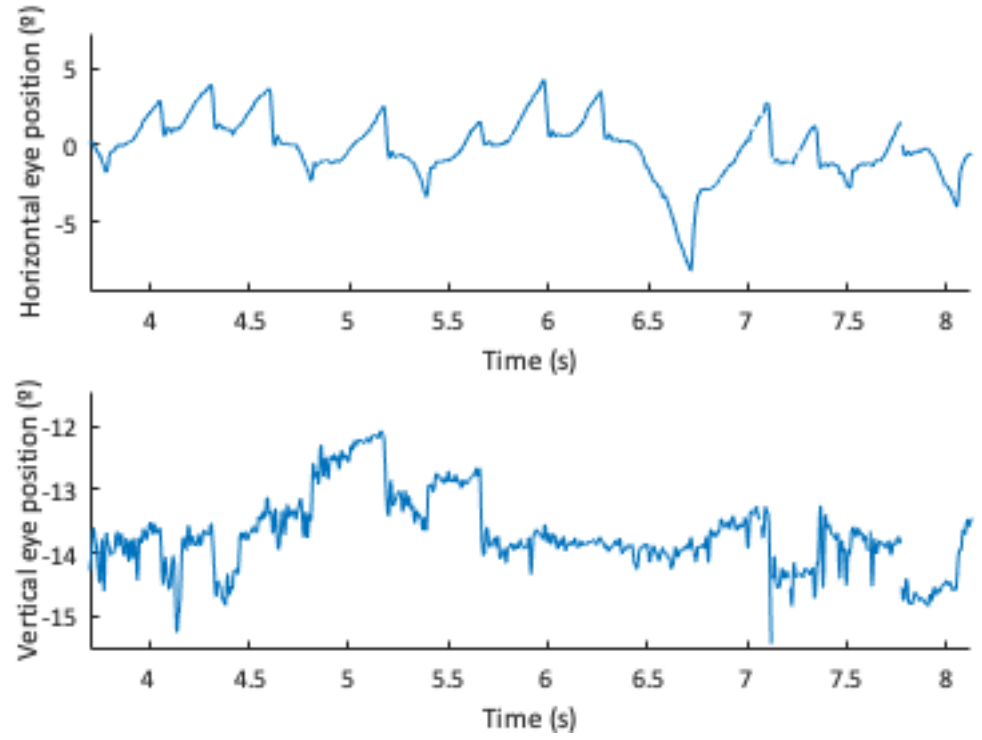
P53


Horizontal eye position (º)
5
0
-5
6.5
7
7.5
8
8.5
9
9.5
10
Time (s)
Vertical eye position (º)
-4
-6
-8
-10
-12
-14
6.5
7
7.5
8
8.5
9
9.5
Time (s)

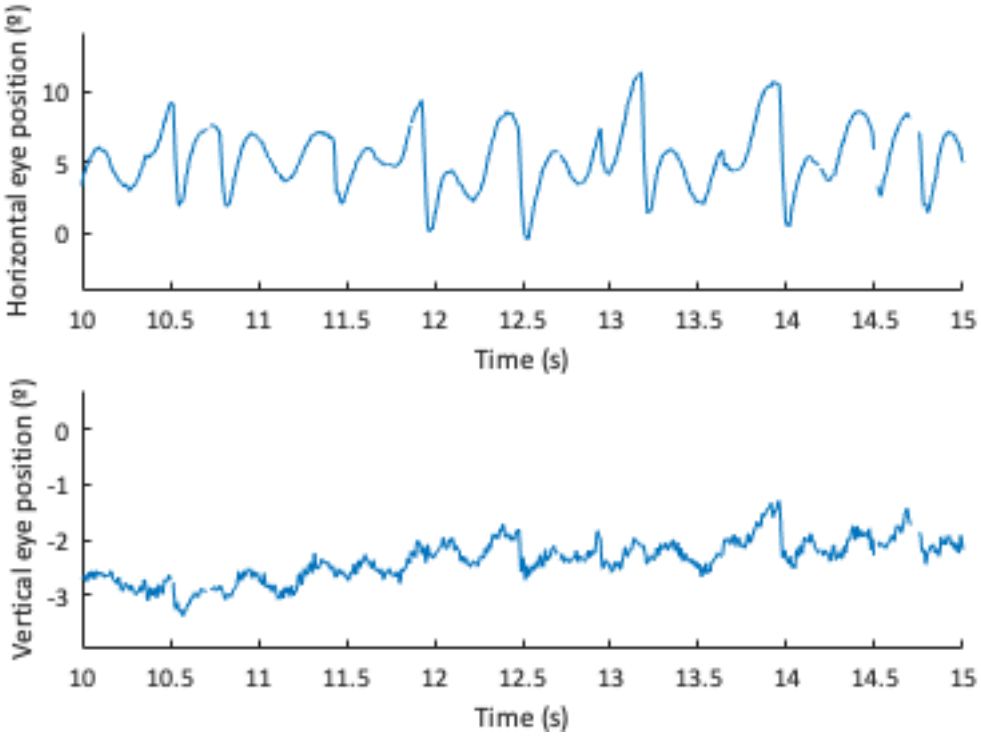
P58


Horizontal eye position (º)
20
10
0
-10
-20
10.5
11
11.5
12
12.5
13
13.5
14
14.5
15
Time (s)
Vertical eye position (º)
-5
-10
-15
-20
10
10.5
11
11.5
12
12.5
13
13.5
14
14.5
15
Time (s)

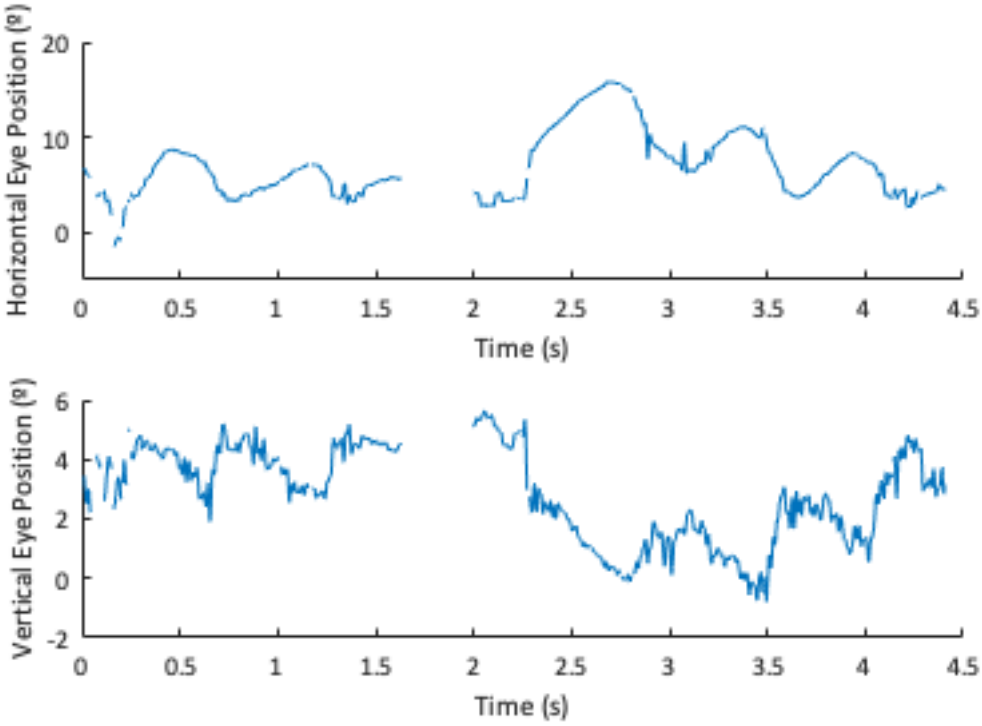
P59


Horizontal eye position (º)
5
0
-5
4
4.5
5
5.5
6
6.5
7
7.5
8
Time (s)
Vertical eye position (º)
-12
-13
-14
-15
4
4.5
5
5.5
6
6.5
7
7.5
8
Time (s)

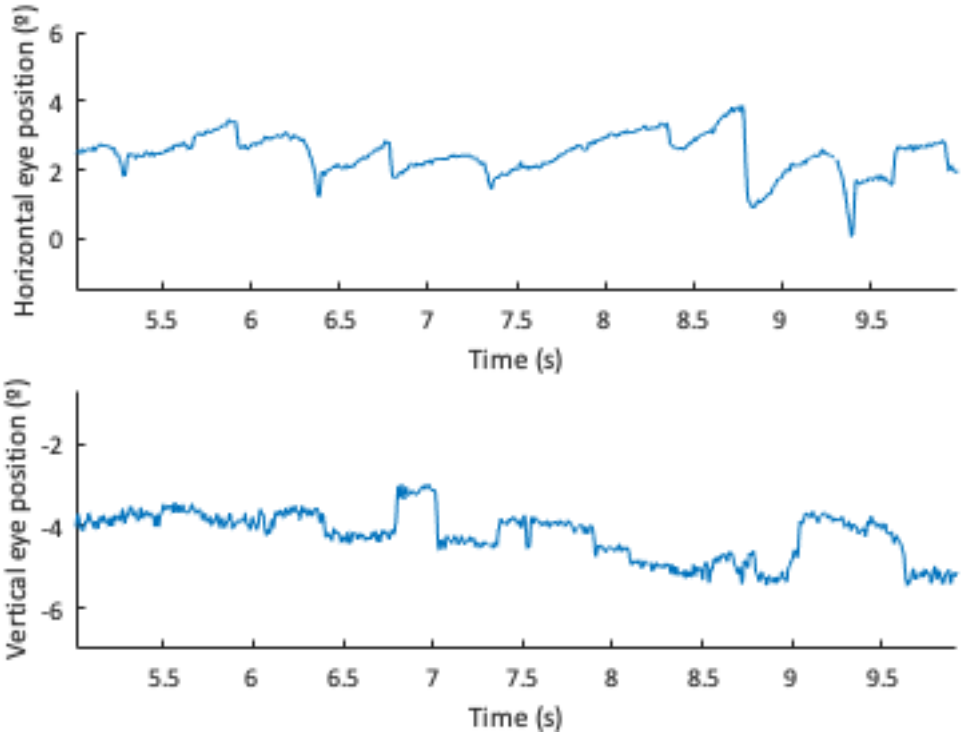
P71


Horizontal eye position (º)
10
5
0
10 10.5 11 11.5 12 12.5 13 13.5 14 14.5 15
Time (s)
Vertical eye position (º)
0
-1
-2
-3
10 10.5 11 11.5 12 12.5 13 13.5 14 14.5 15
Time (s)

P74

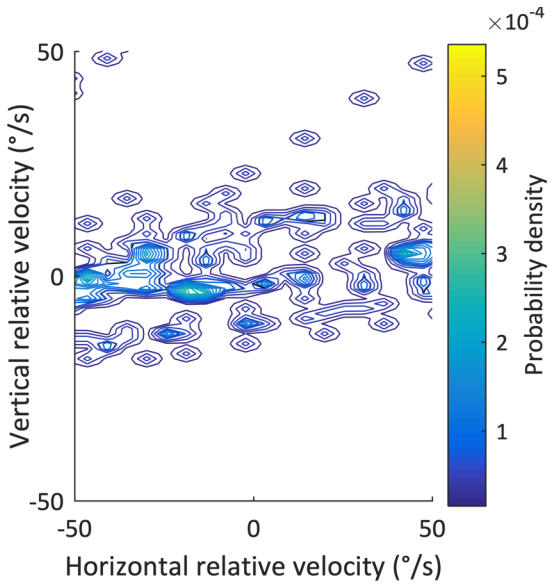

Horizontal Eye Position (º)
20
10
0
0 0.5 1 1.5 2 2.5 3 3.5 4 4.5
Time (s)
Vertical Eye Position (º)
6
4
2
0
-2
0 0.5 1 1.5 2 2.5 3 3.5 4 4.5
Time (s)

P80

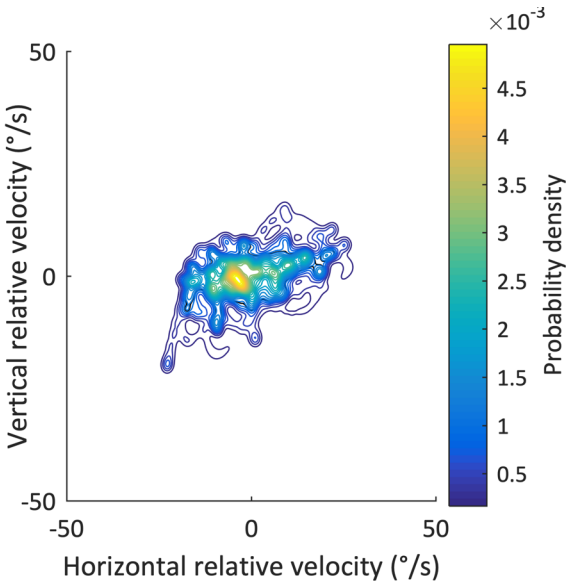

Horizontal eye position (º)
6
4
2
0
5.5
6
6.5
7
7.5
8
8.5
9
9.5
Time (s)
Vertical eye position (º)
-2
-4
-6
5.5
6
6.5
7
7.5
8
8.5
9
9.5
Time (s)

Appendix K: PDF during fixation of children with DS and nystagmus (DSN)

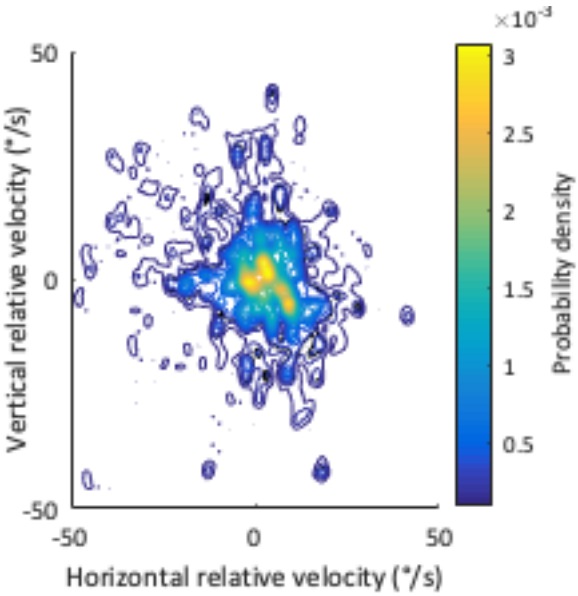
P15



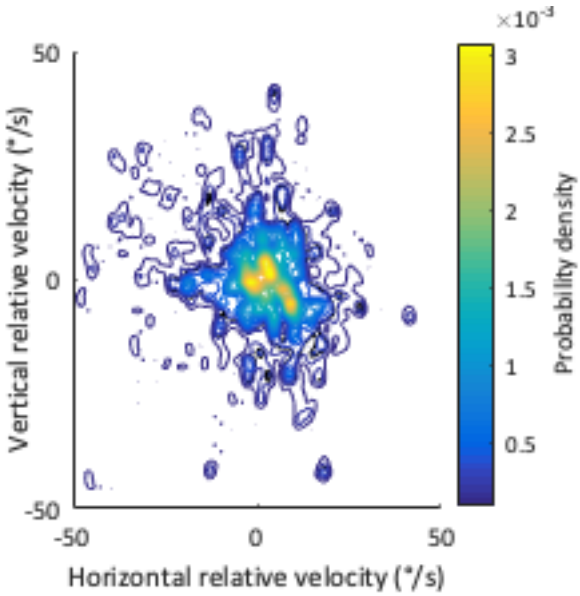
P22



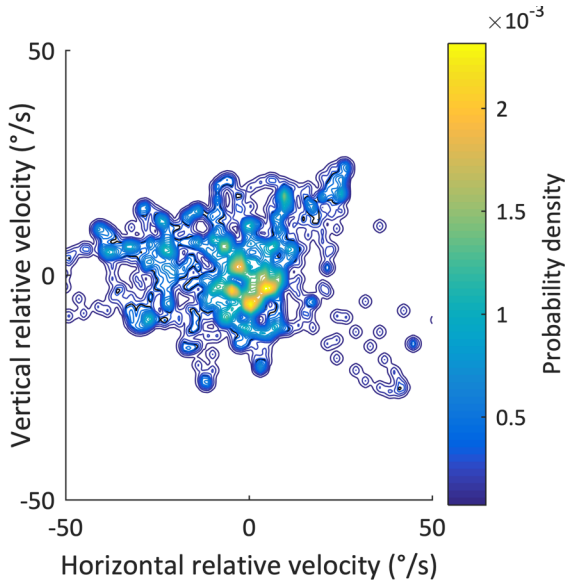
P31



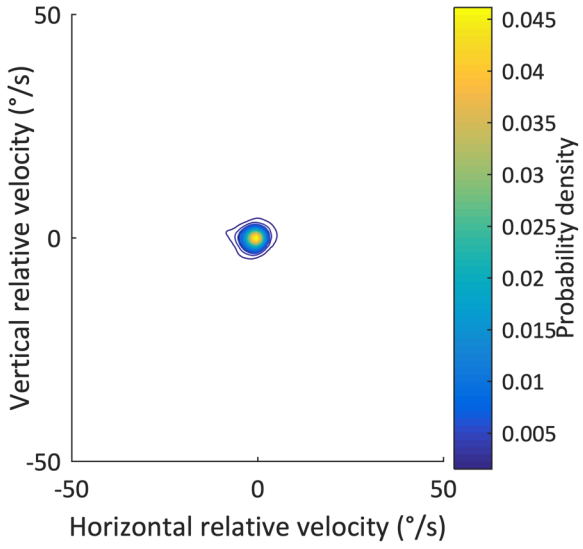
P36



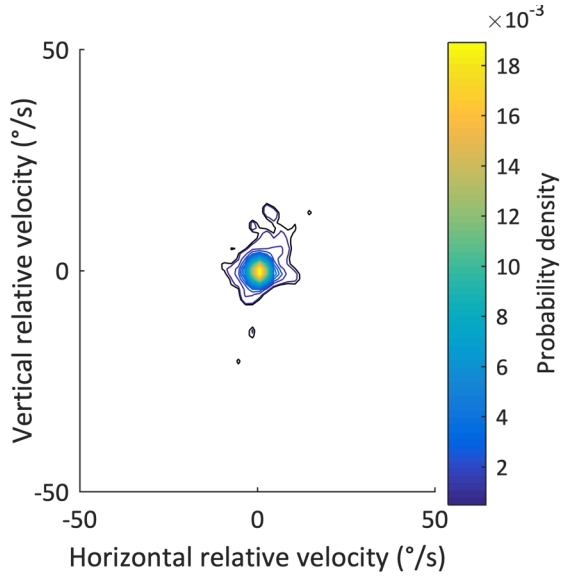
P67



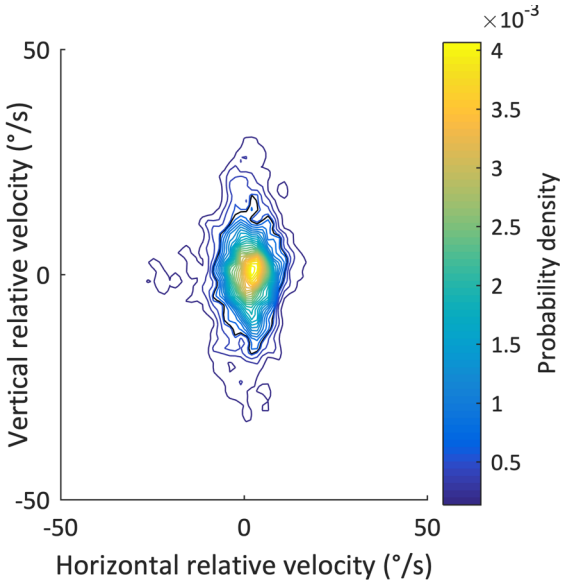
P72



P81

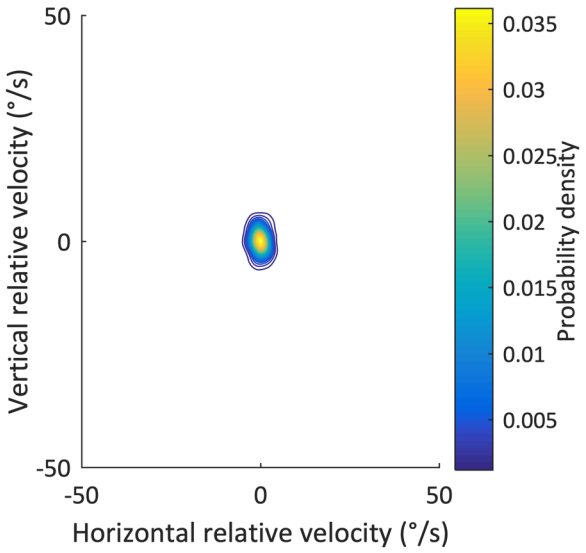


P82

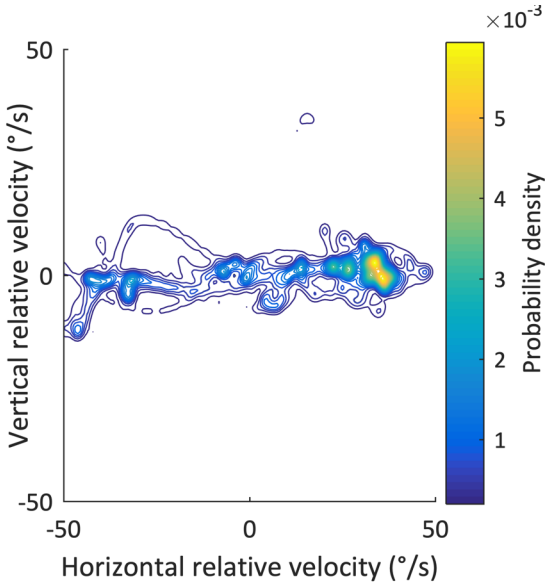


Appendix L: PDF during fixation of typically developing children with nystagmus (TN)

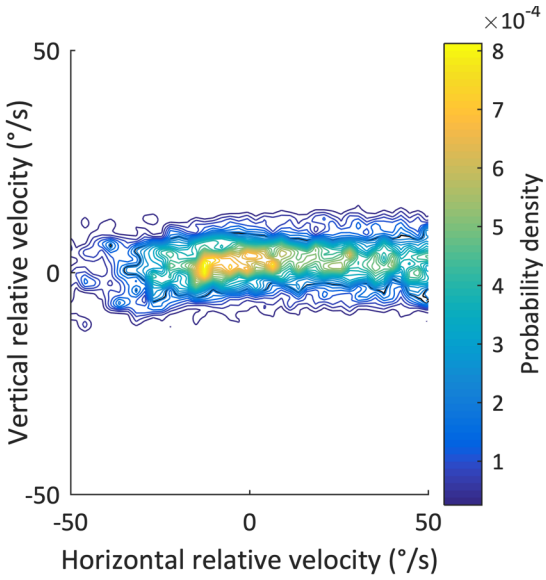
P04



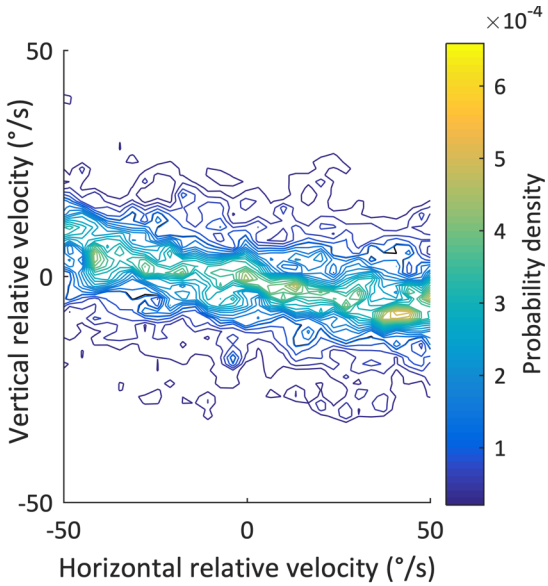
P14



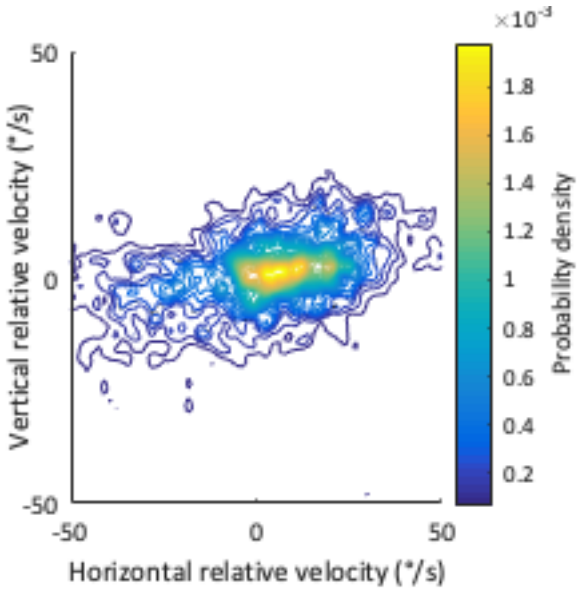
P53



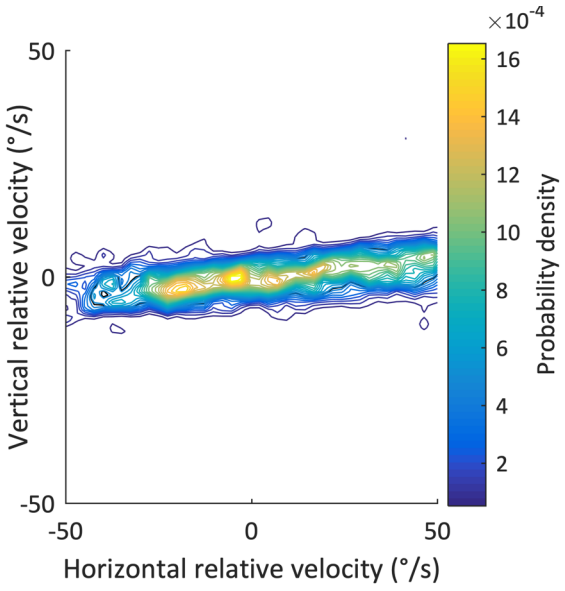
P58



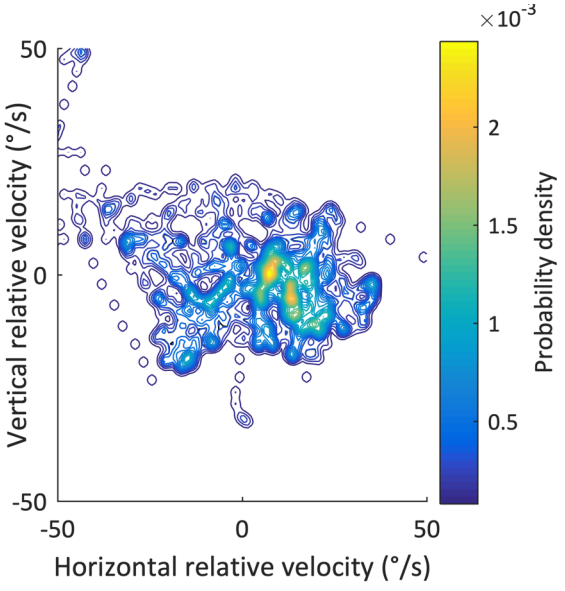
P59



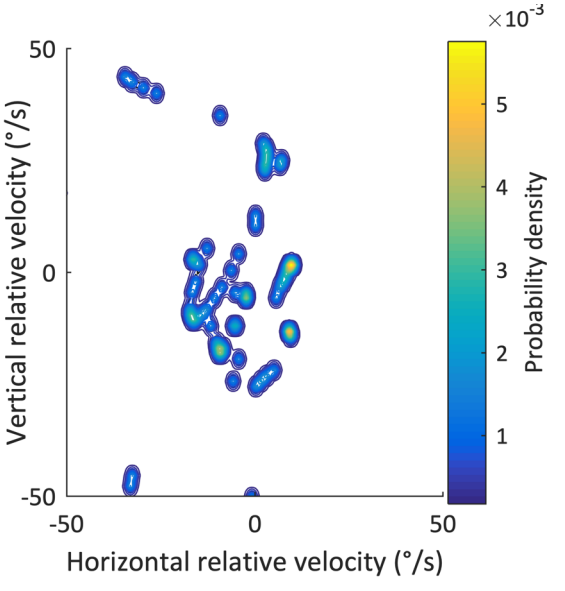
P71



P74

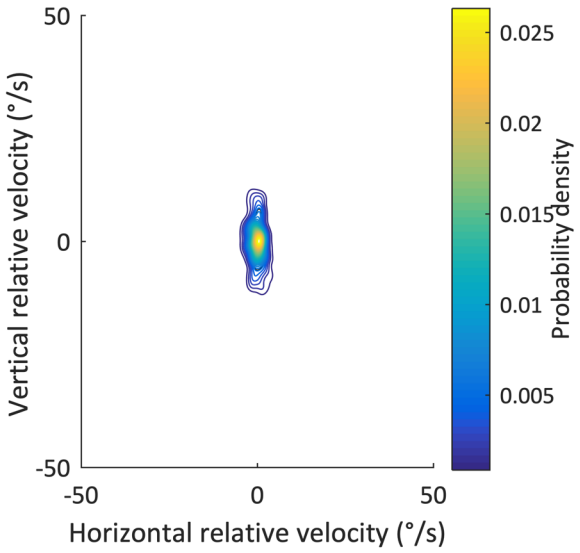


P80

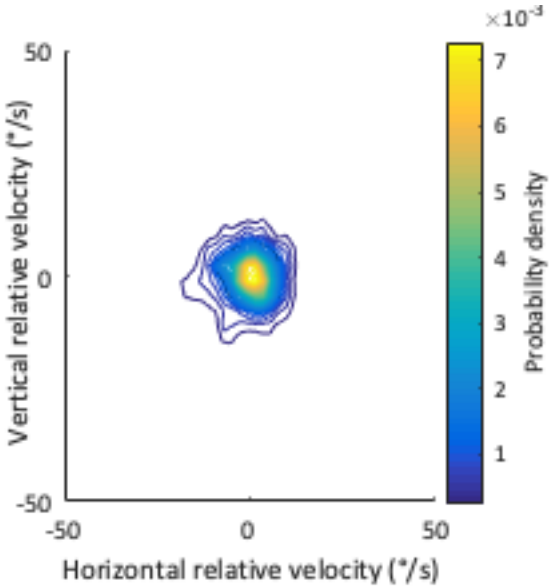


Appendix M: PDF during fixation of children with DS and without nystagmus (DS)

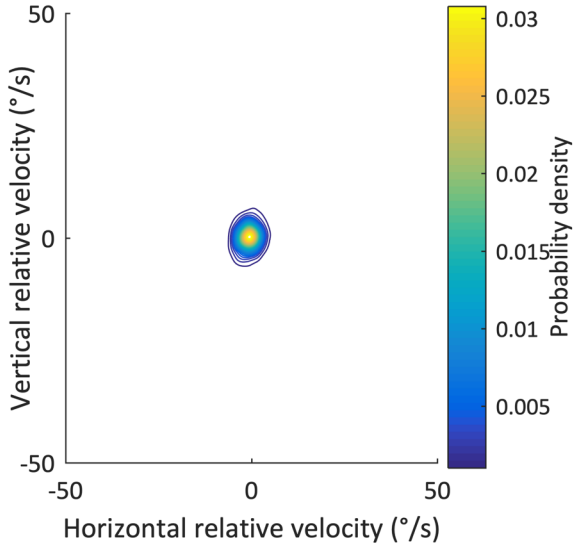
P01



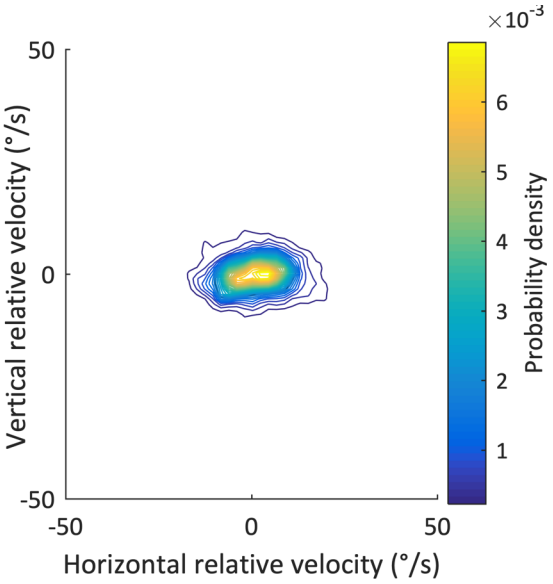
P03



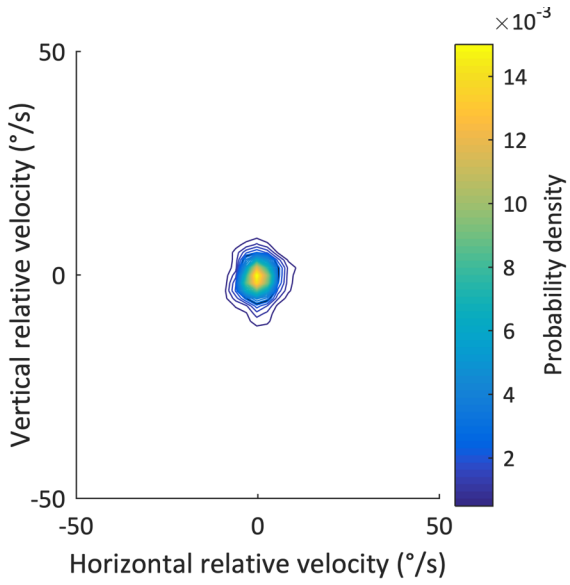
P08



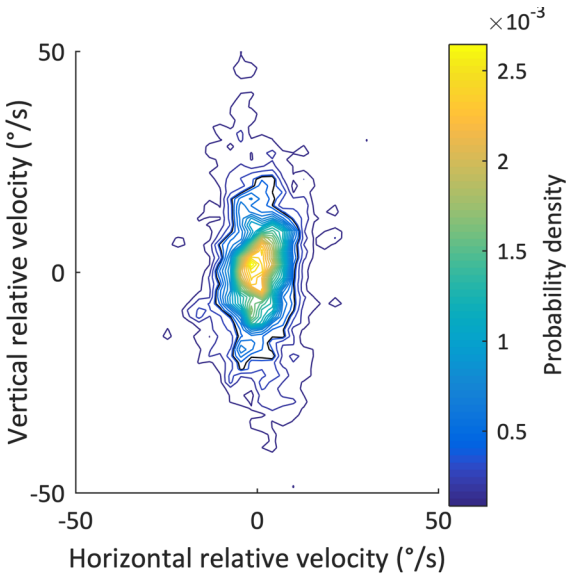
P09



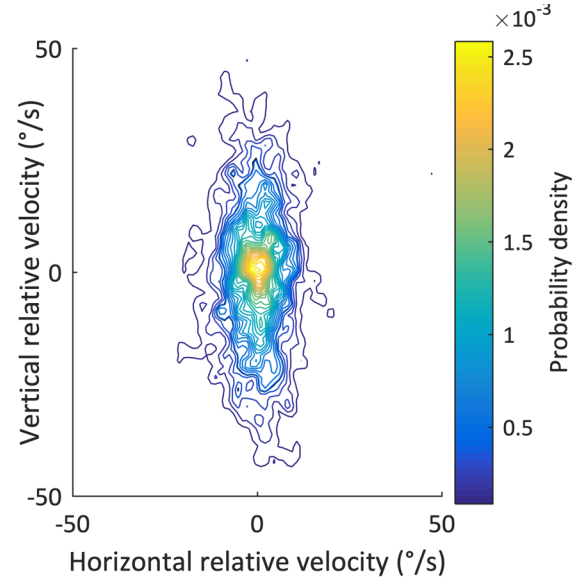
P20



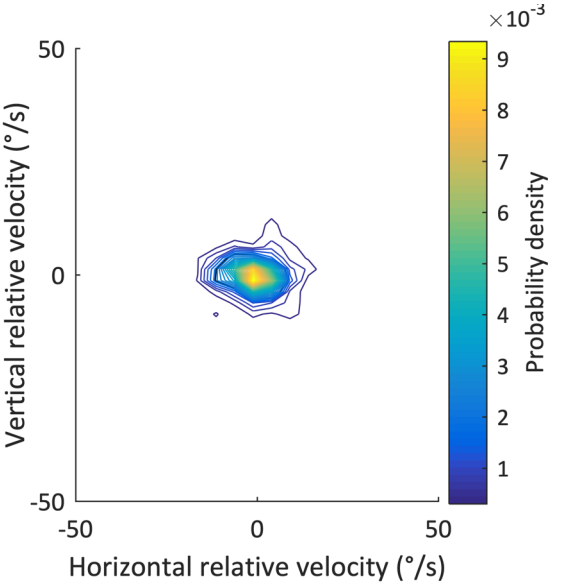
P23



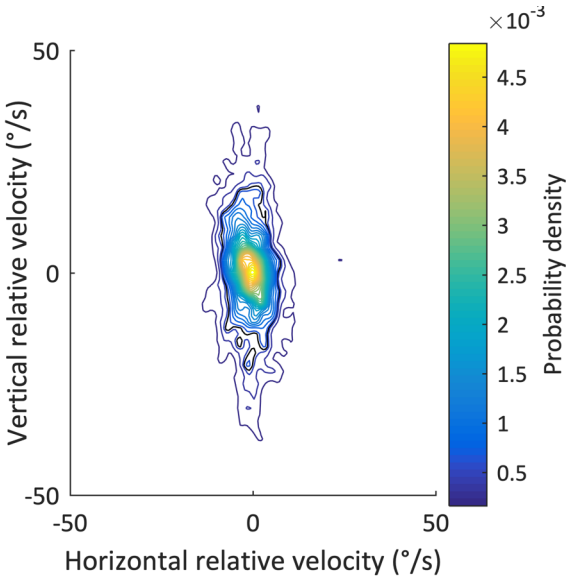
P26



P35

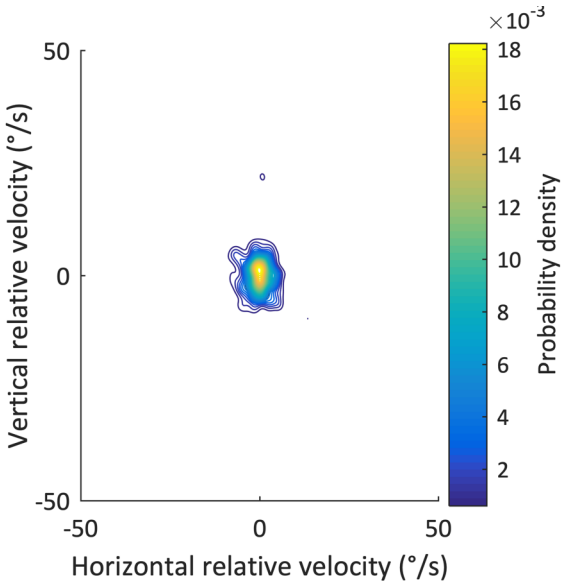


P42

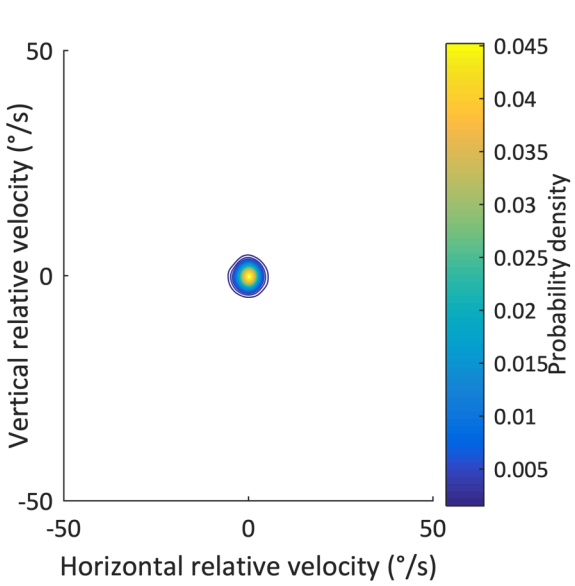

×10^-3
4.5
4
3.5
3
2.5
2
1.5
1
0.5
Probability density
50
0
-50
Vertical relative velocity (°/s)
-50
0
50
Horizontal relative velocity (°/s)

Appendix N: PDF during fixation of typically developing children with no nystagmus (T)

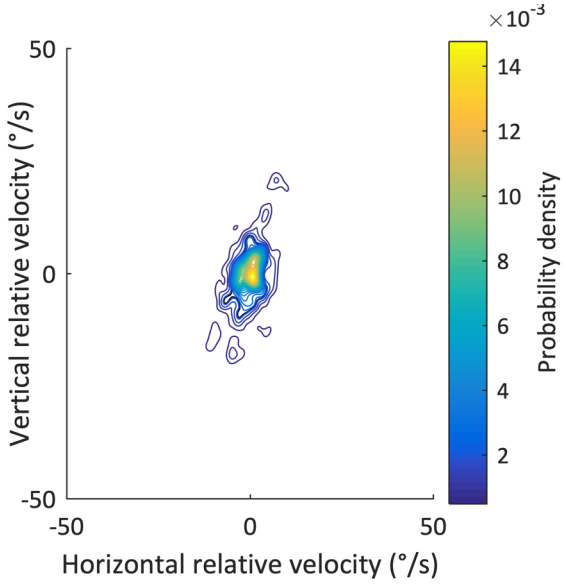
P02



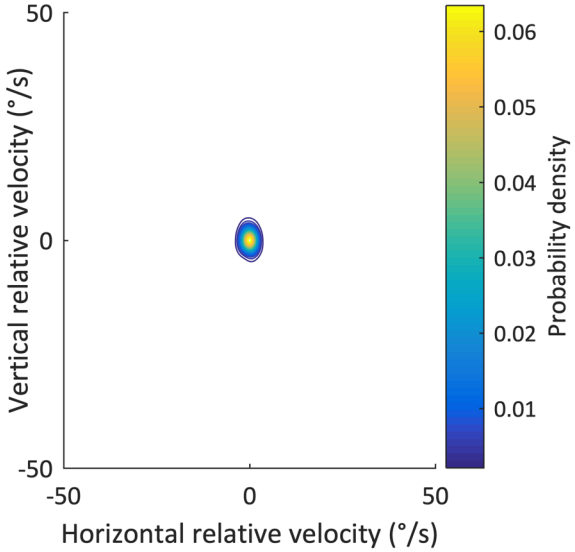
P10



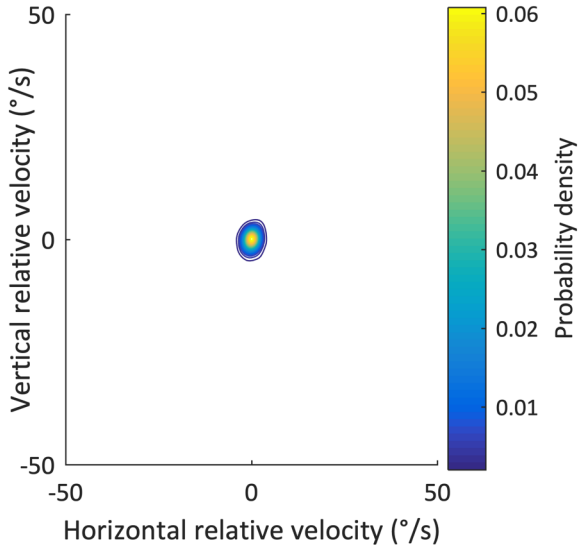
P12



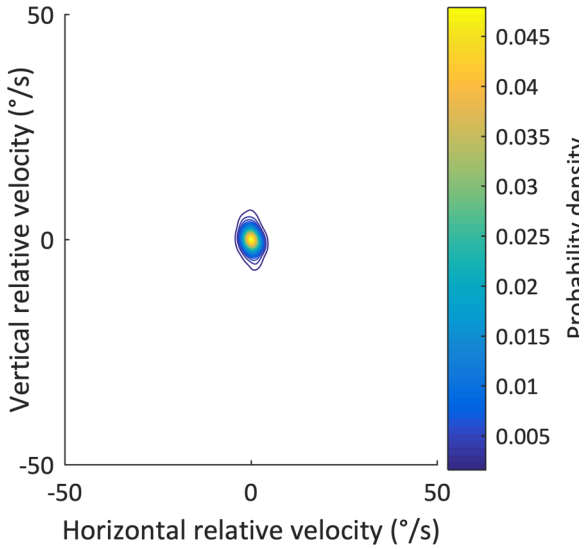
P24



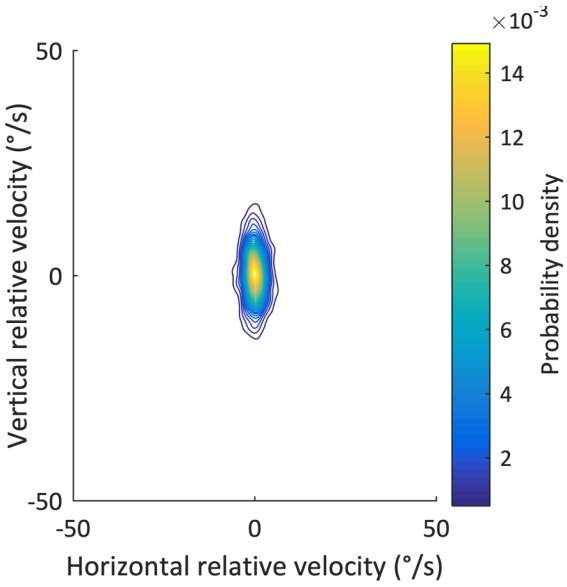
P27



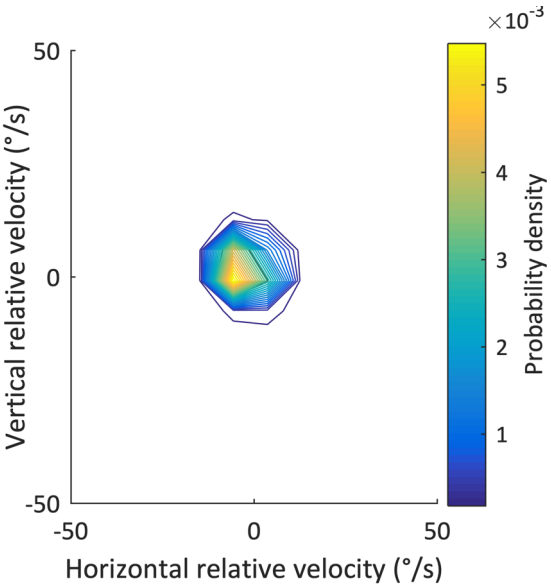
P28



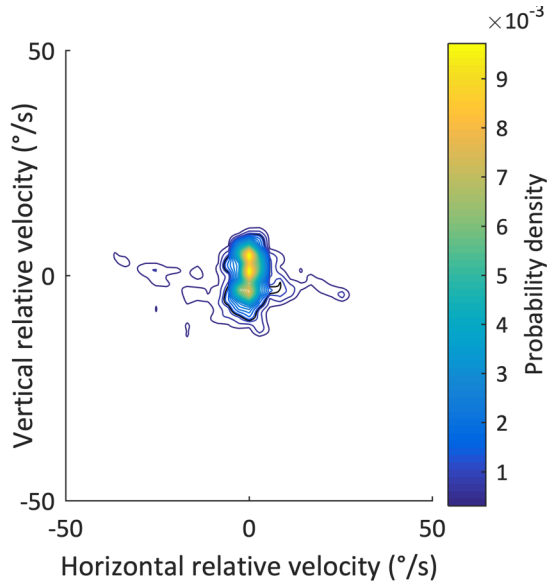
P41



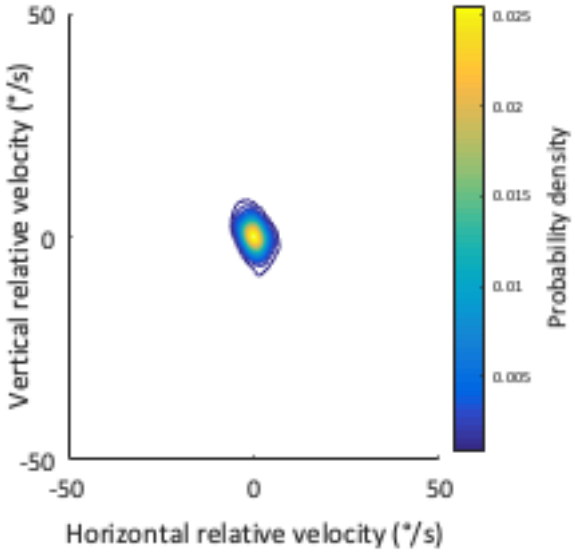
P43



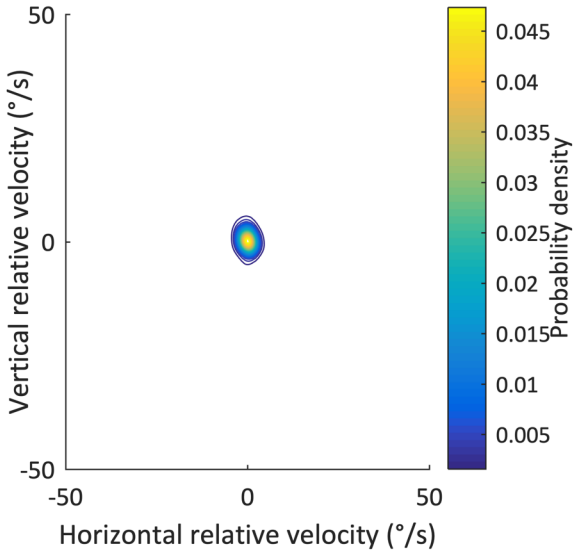
P45



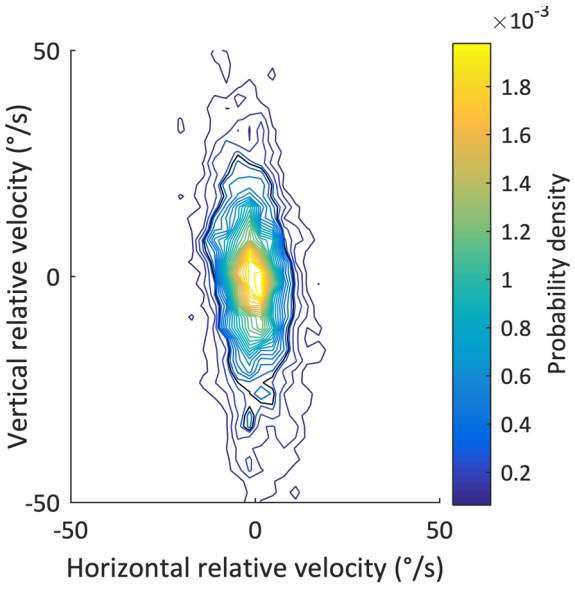
P47



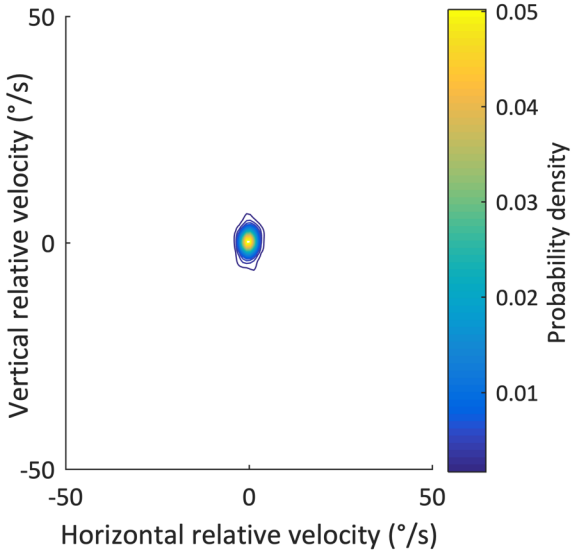
P63



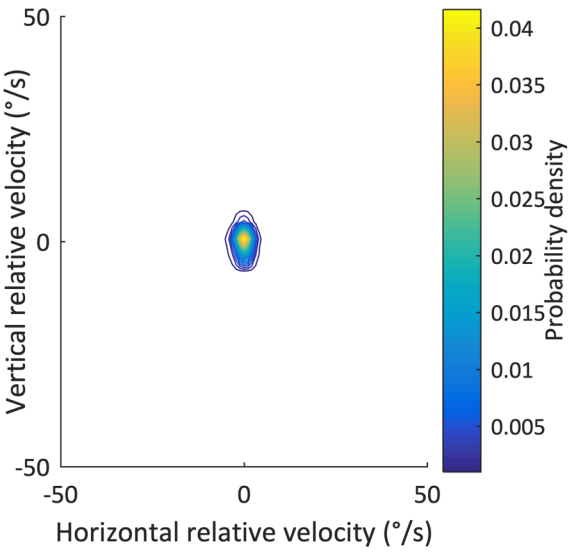
P65



P66

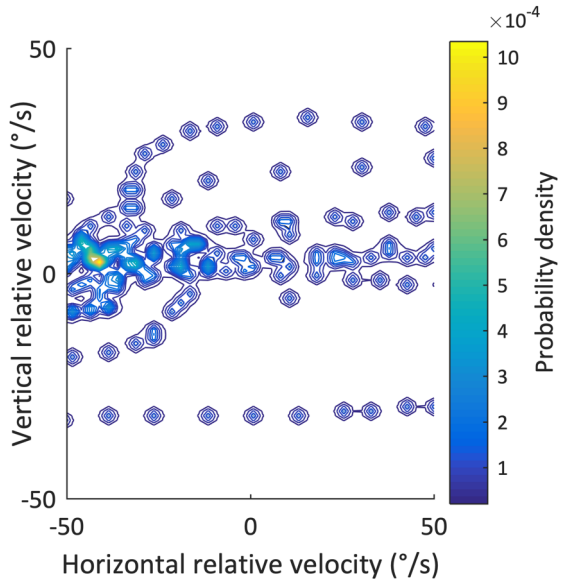

50
0
-50
-50
0
50
Vertical relative velocity (°/s)
Horizontal relative velocity (°/s)
0.05
0.04
0.03
0.02
0.01
Probability density

P84

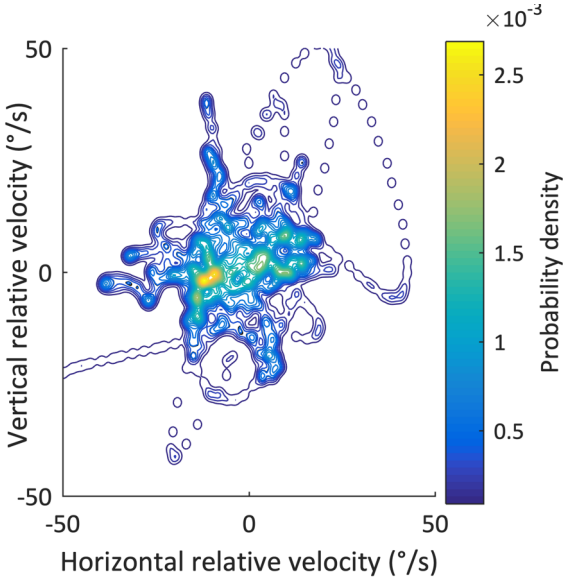

50
0
-50
-50
0
50
Vertical relative velocity (°/s)
Horizontal relative velocity (°/s)
0.04
0.035
0.03
0.025
0.02
0.015
0.01
0.005
Probability density

Appendix O: PDF during rightward pursuit of children with DS and nystagmus (DSN)

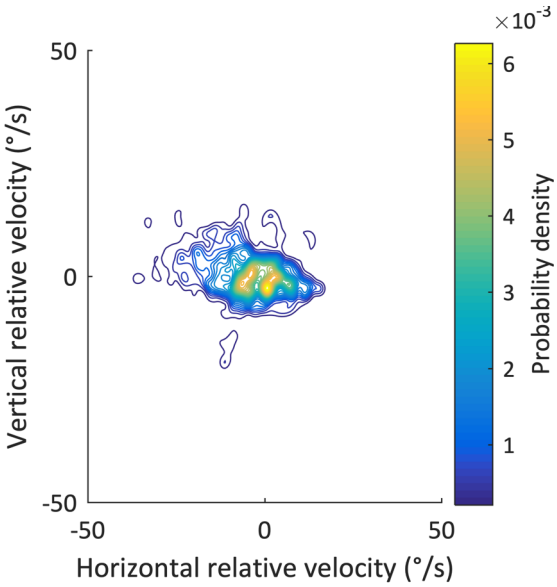
P15



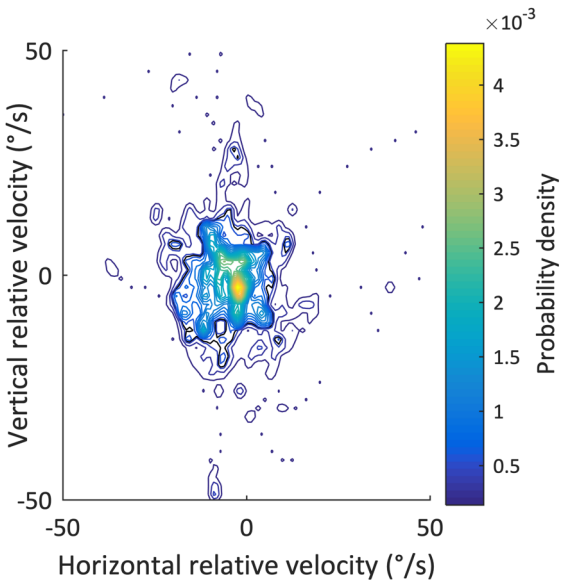
P22



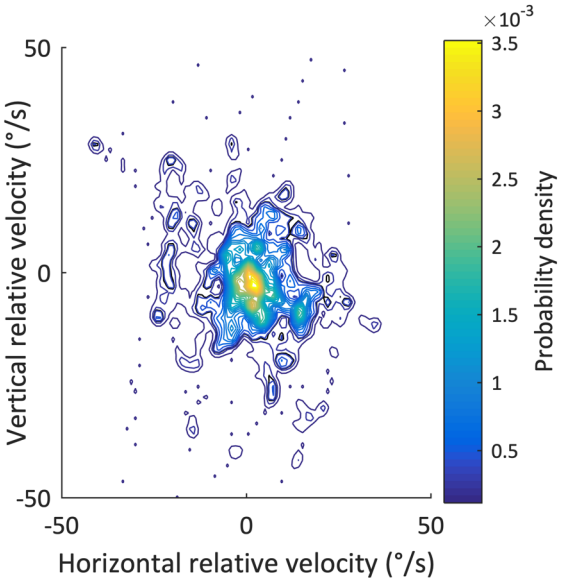
P31



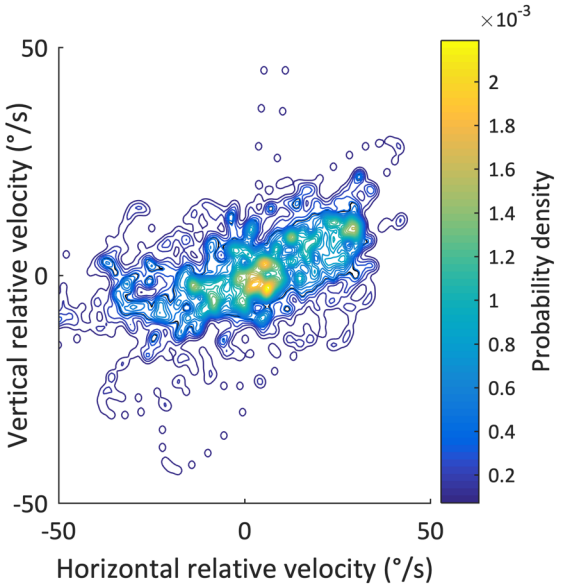
P34



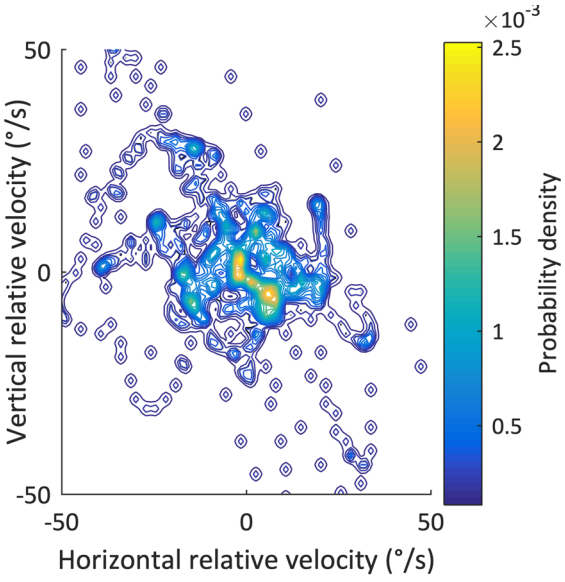
P36



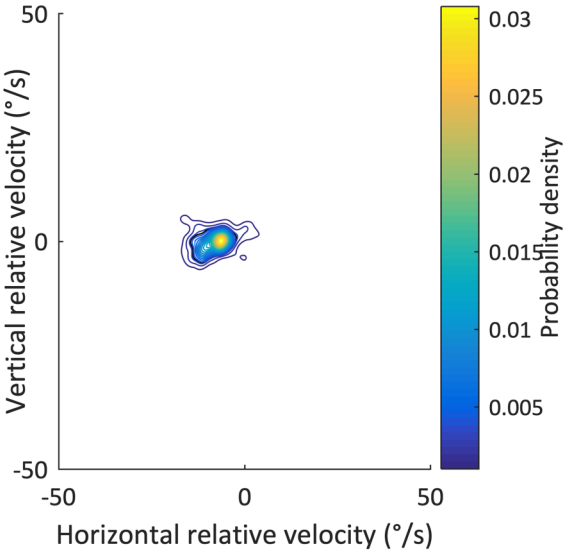
P52



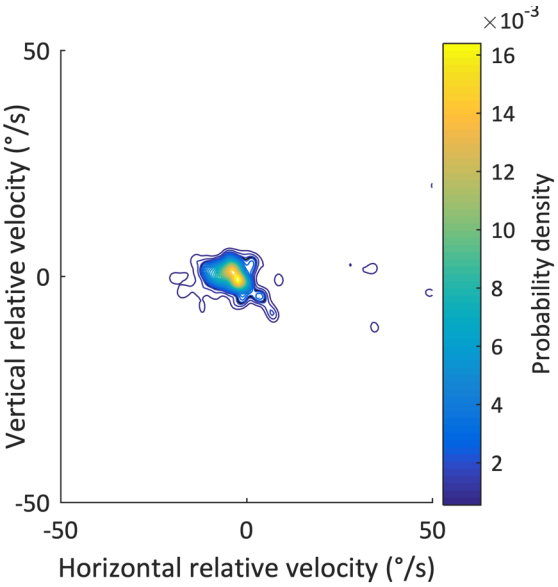
P67



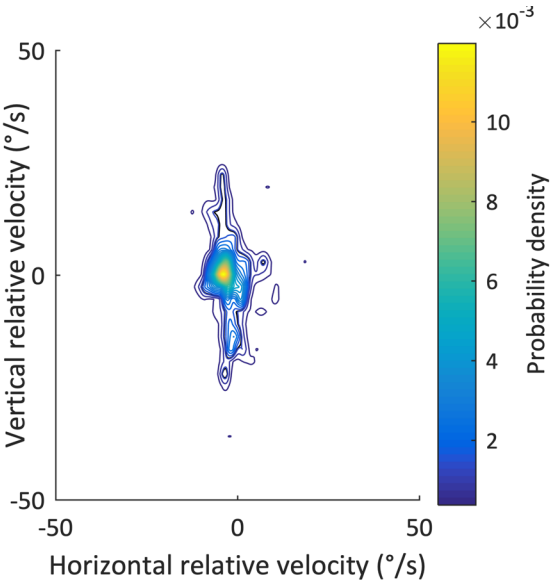
P72



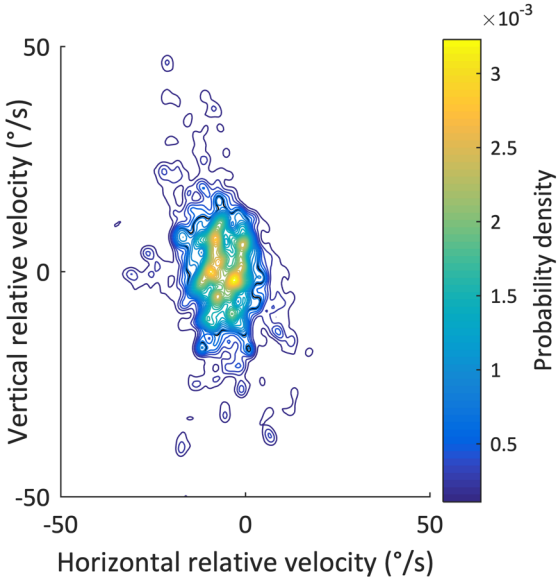
P75


×10^-3
16
14
12
10
8
6
4
2
Probability density
50
0
-50
Vertical relative velocity (°/s)
-50
0
50
Horizontal relative velocity (°/s)

P81

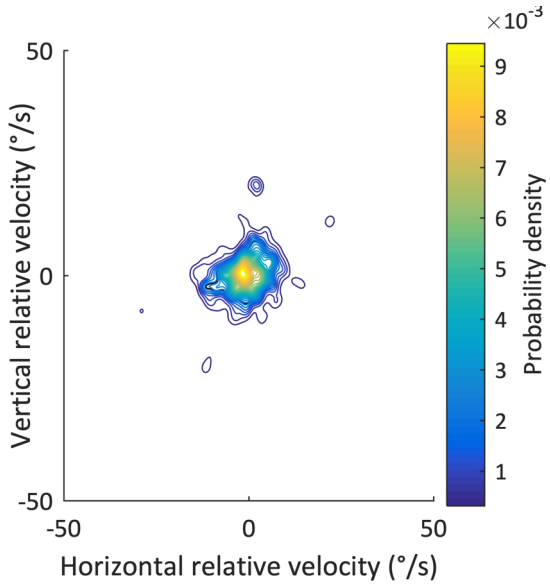

×10^-3
10
8
6
4
2
Probability density
50
0
-50
Vertical relative velocity (°/s)
-50
0
50
Horizontal relative velocity (°/s)

P82

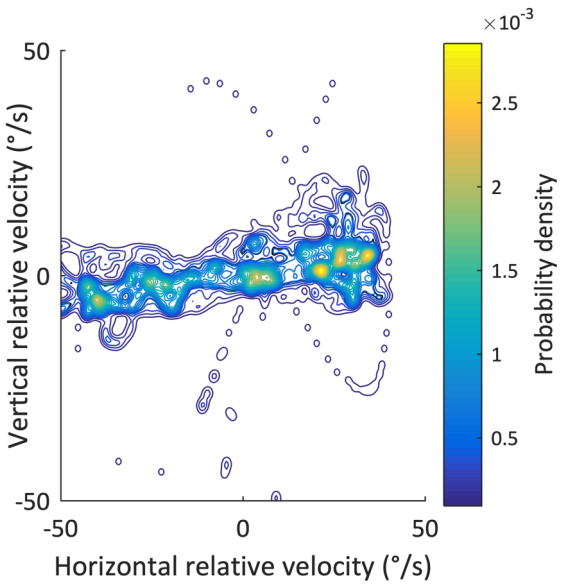

×10^-3
3
2.5
2
1.5
1
0.5
Probability density
50
0
-50
Vertical relative velocity (°/s)
-50
0
50
Horizontal relative velocity (°/s)

Appendix P: PDF during rightward pursuit of typically developing children with nystagmus (TN)

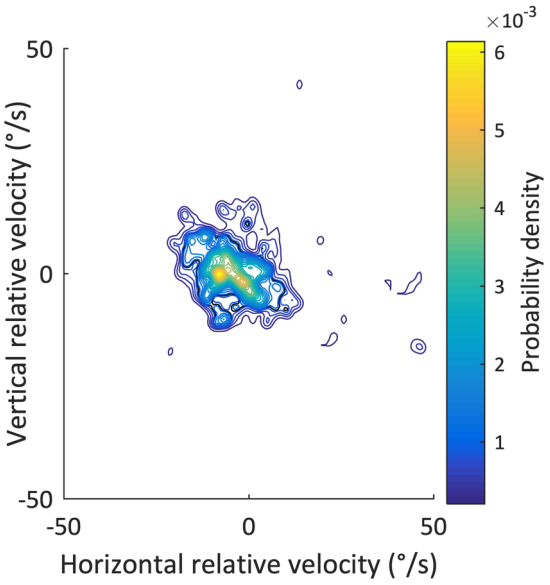
P04



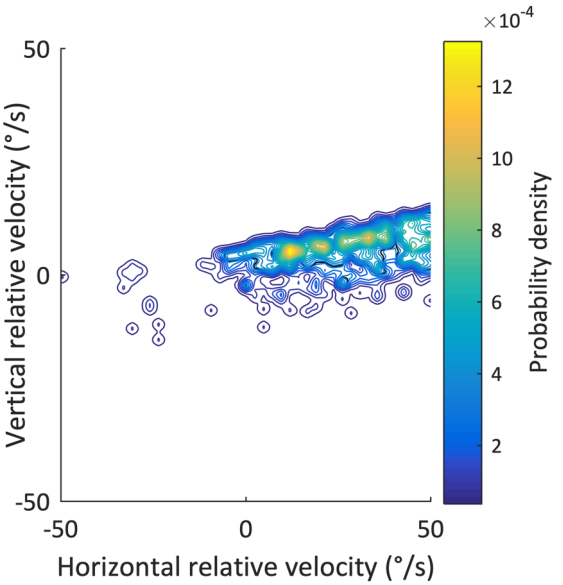
P14



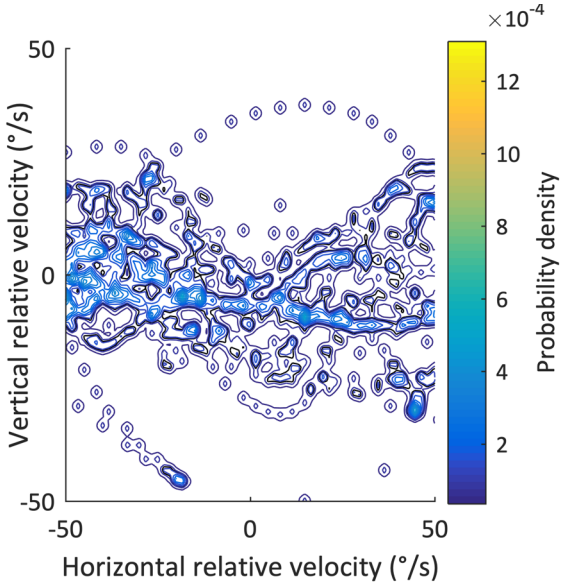
P32



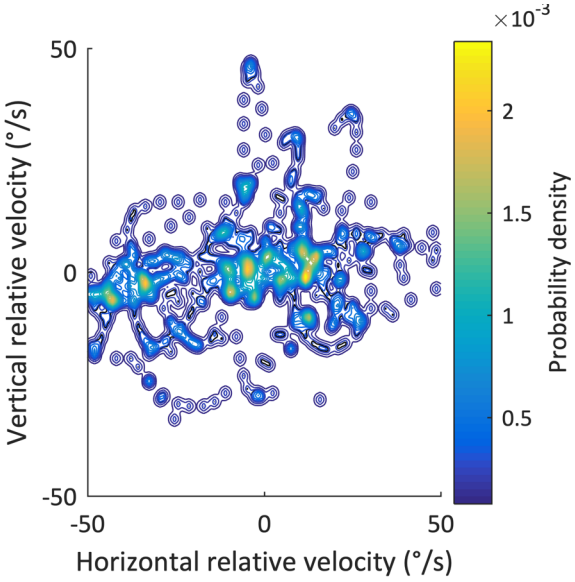
P53



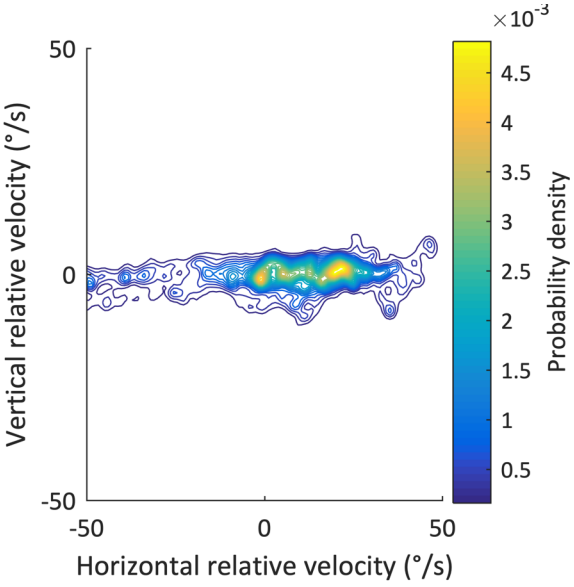
P58



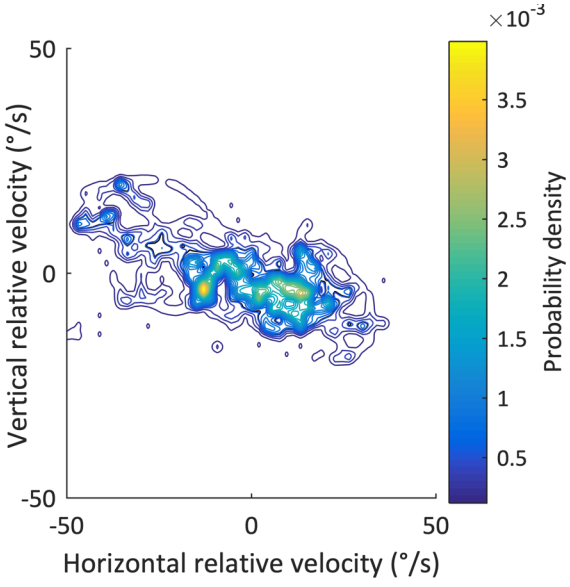
P59



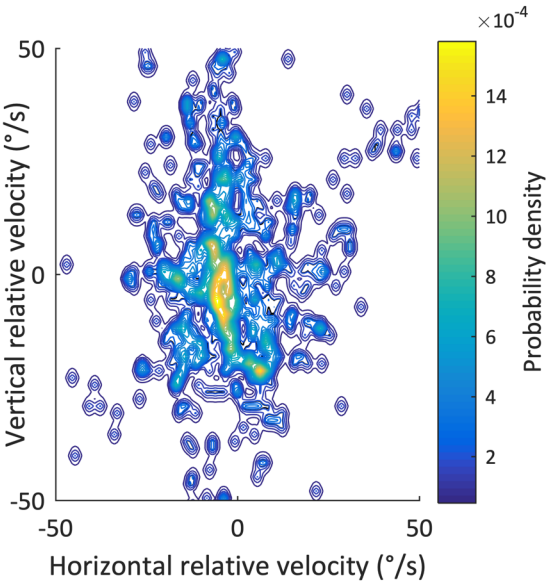
P71



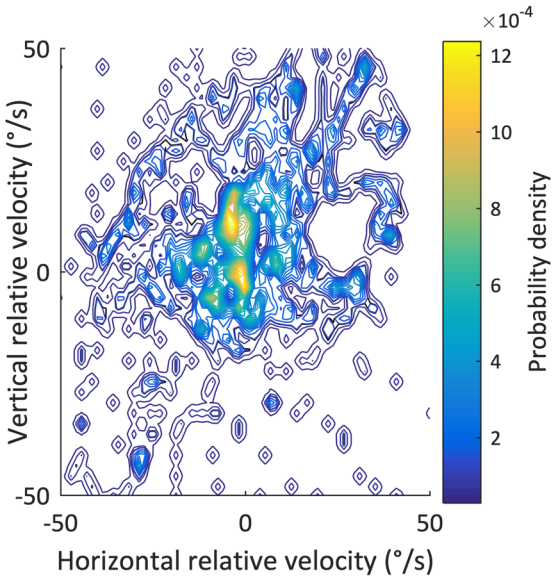
P74



P80

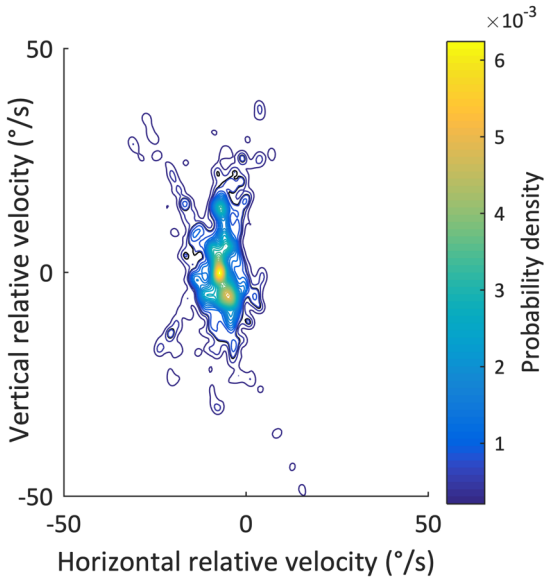

×10^-4
14
12
10
8
6
4
2
Probability density
50
0
-50
Vertical relative velocity (°/s)
-50
0
50
Horizontal relative velocity (°/s)

P83

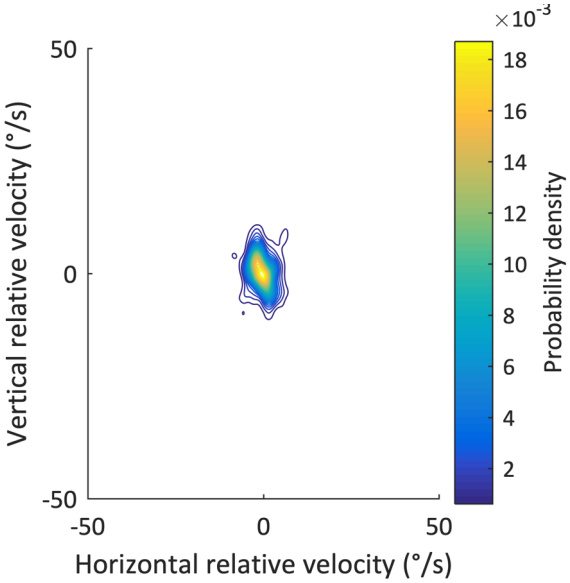

×10^-4
12
10
8
6
4
2
Probability density
50
0
-50
Vertical relative velocity (°/s)
-50
0
50
Horizontal relative velocity (°/s)

Appendix Q: PDF during rightward pursuit of children with DS and without nystagmus (DS)

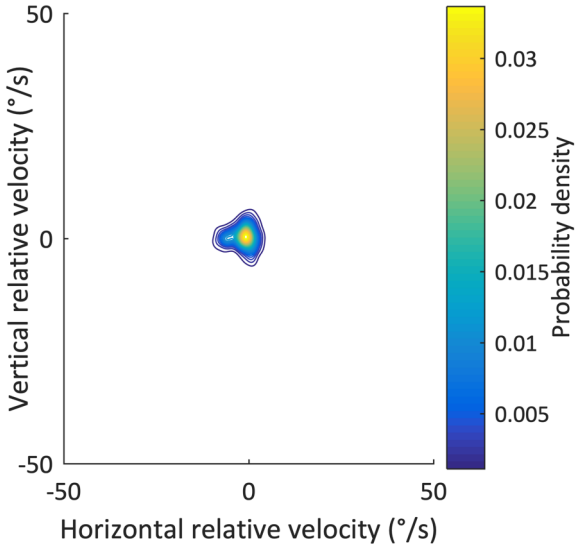
P01



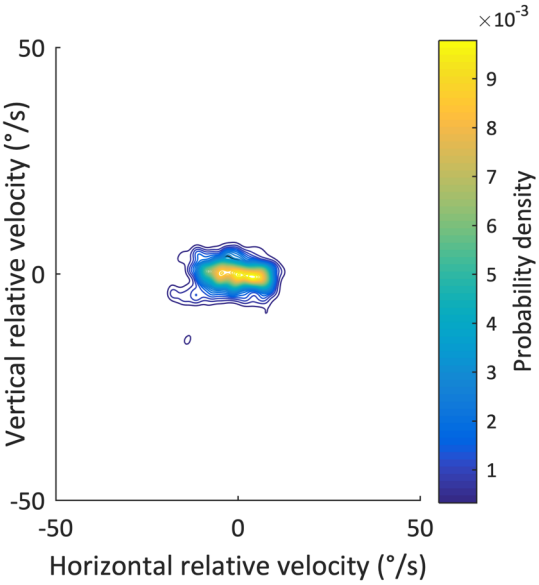
P03



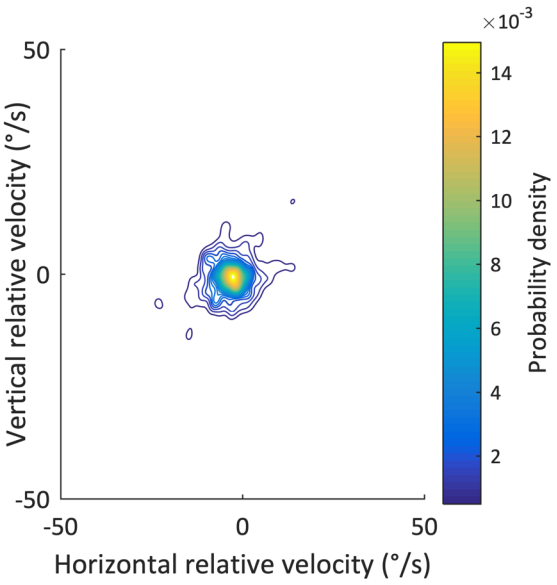
P08



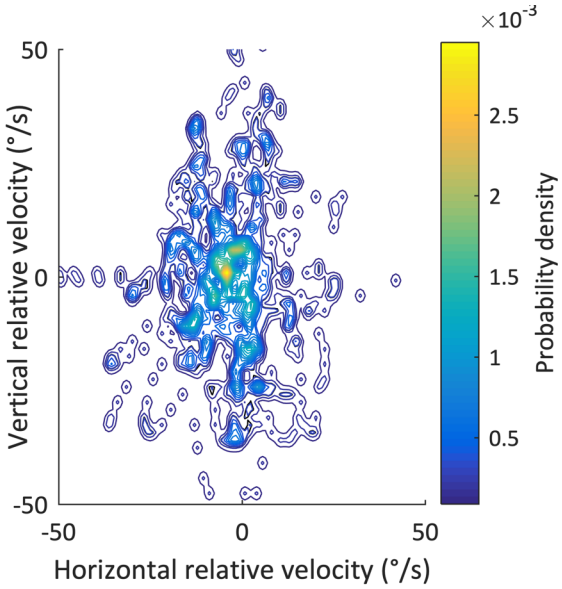
P09



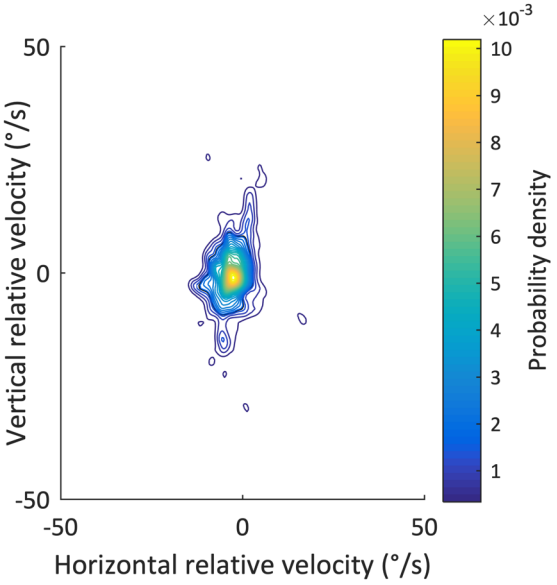
P20



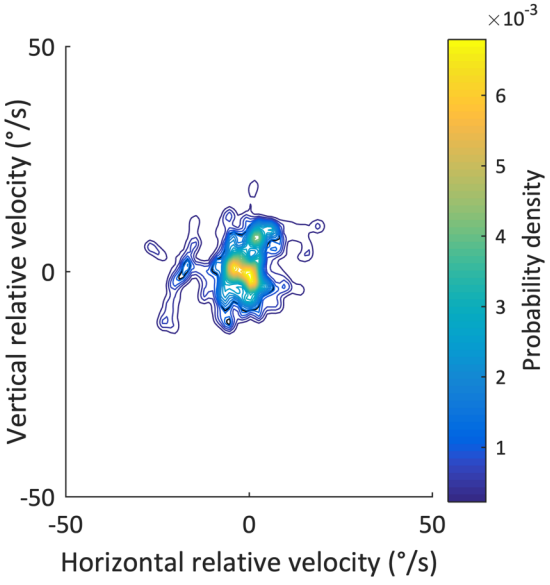
P23

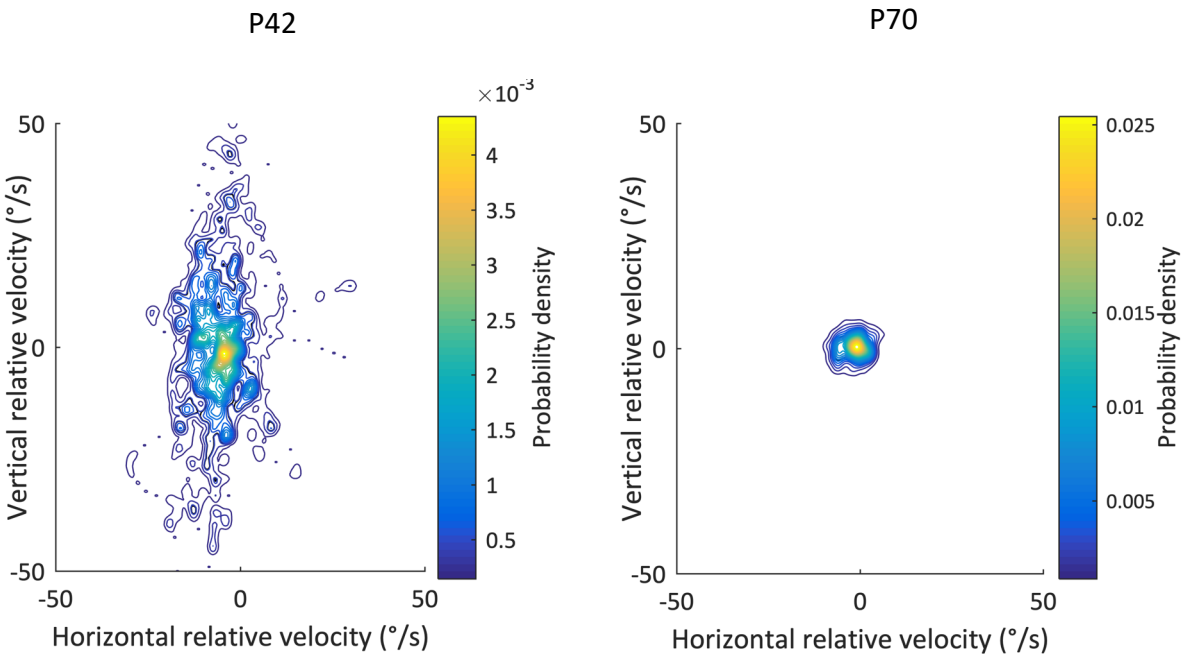


P26



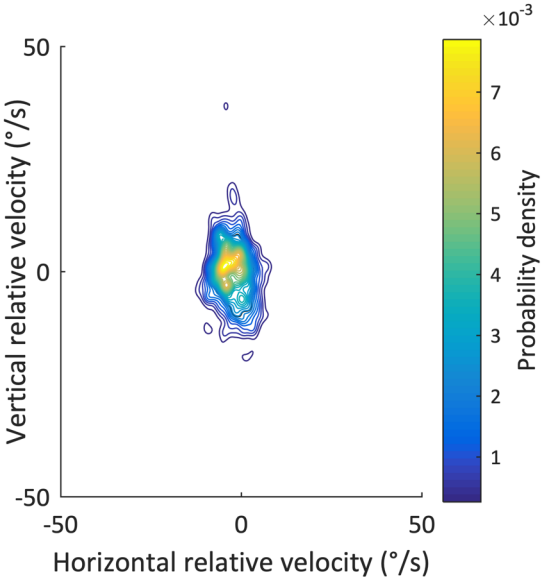
P35



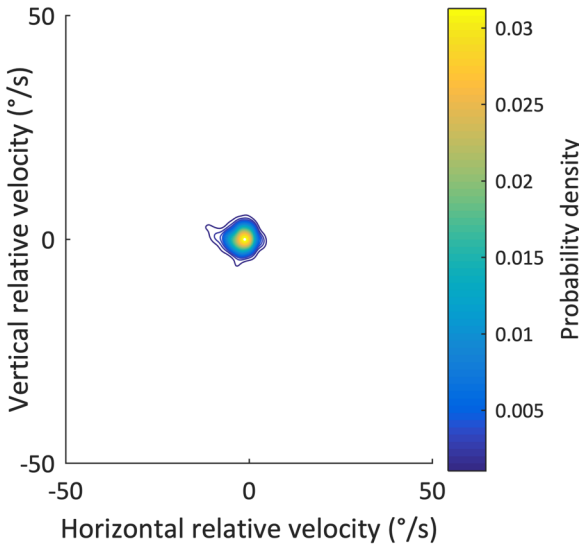

P42
P70
×10^-3
4
3.5
3
2.5
2
1.5
1
0.5
Probability density
0.025
0.02
0.015
0.01
0.005
Probability density
50
0
-50
Vertical relative velocity (°/s)
-50
0
50
Horizontal relative velocity (°/s)

Appendix R: PDF during rightward pursuit of typically developing children with no nystagmus (T)

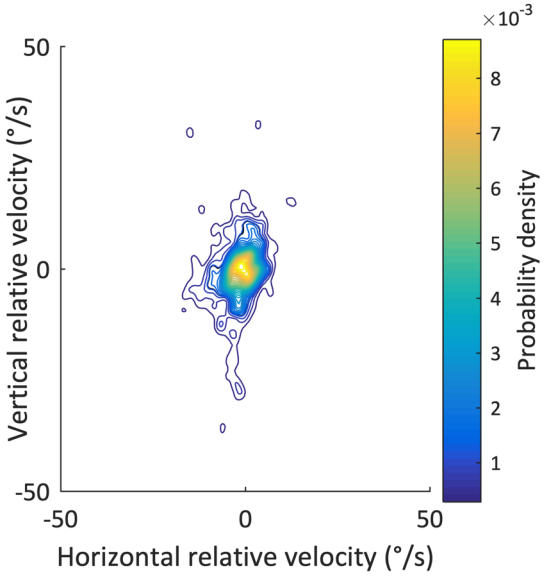
P02



P10



P12



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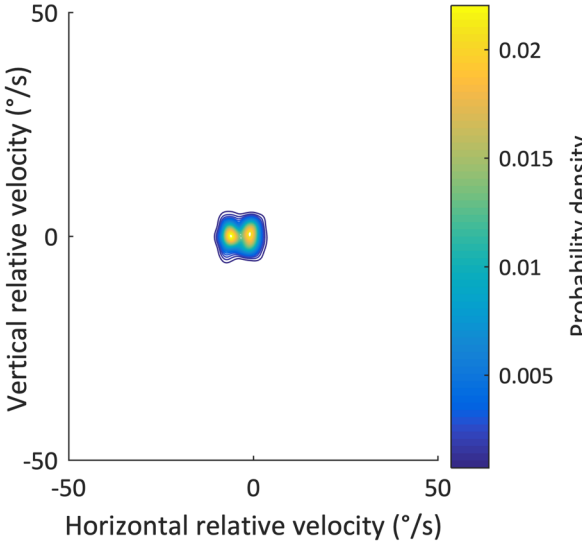

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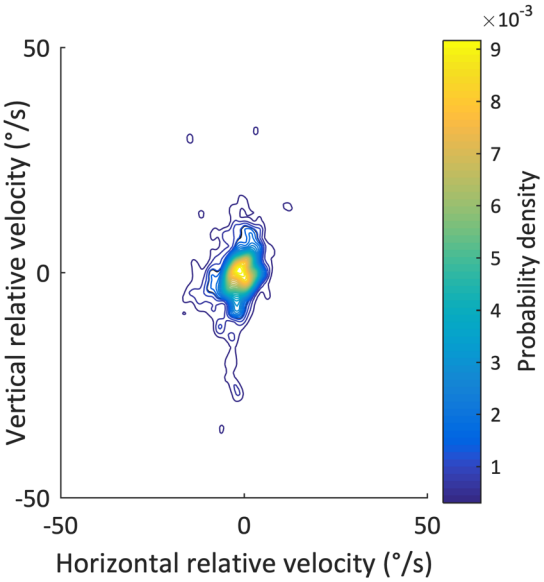

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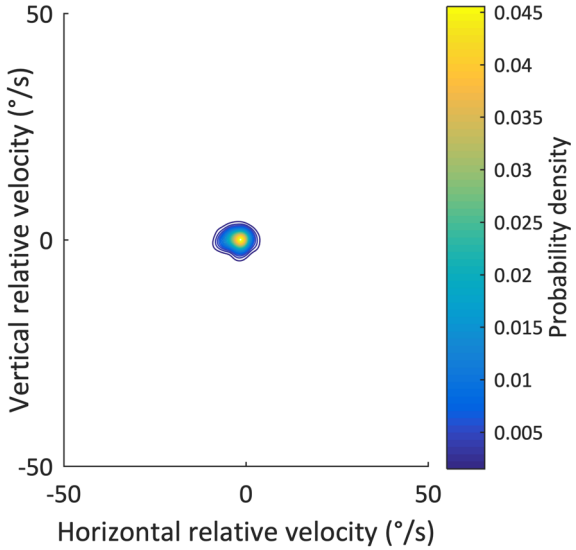

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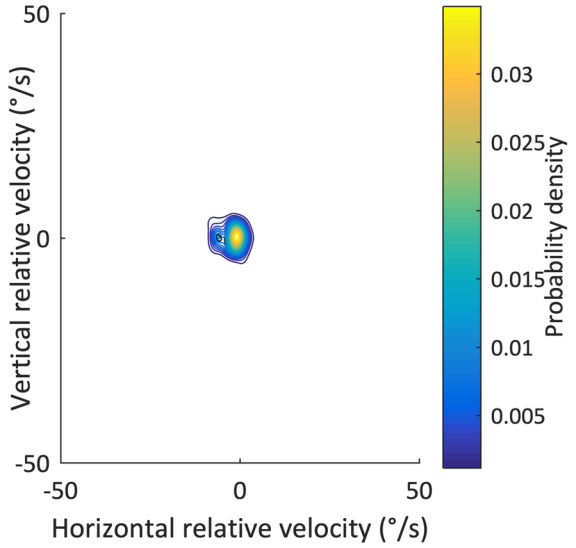

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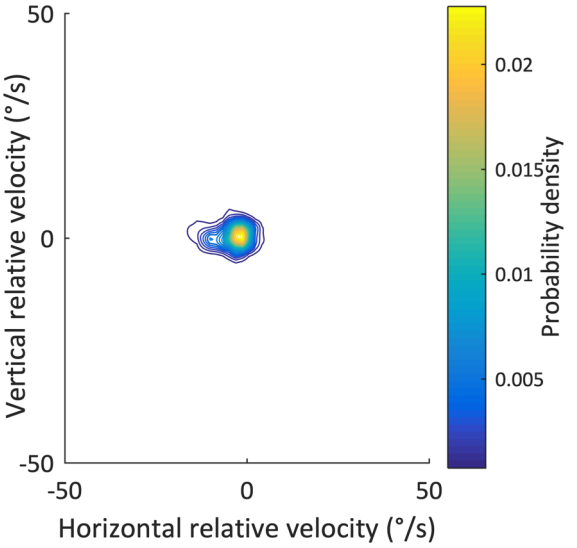

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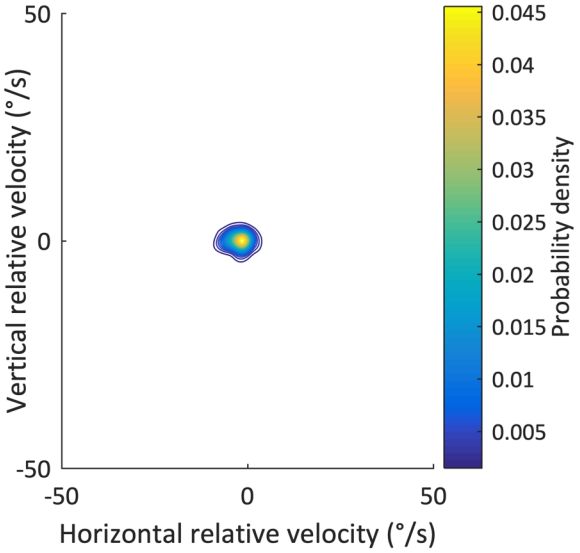

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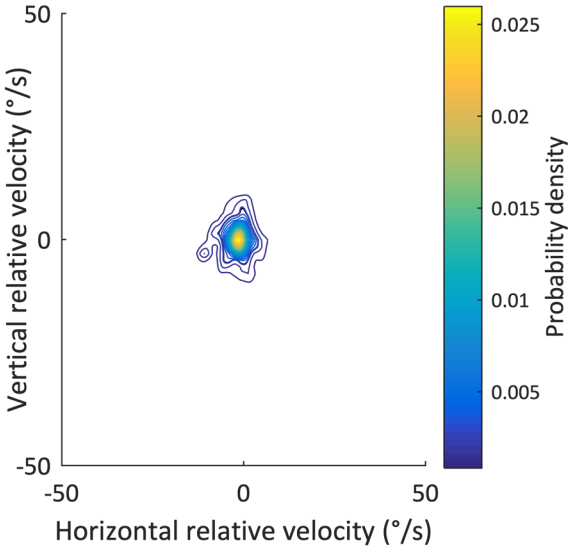

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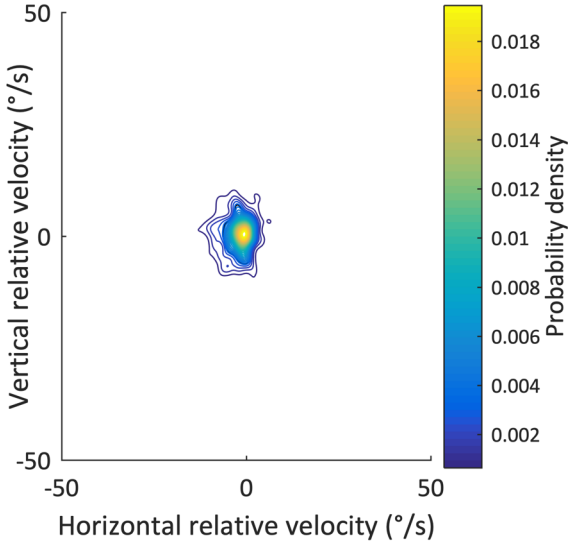

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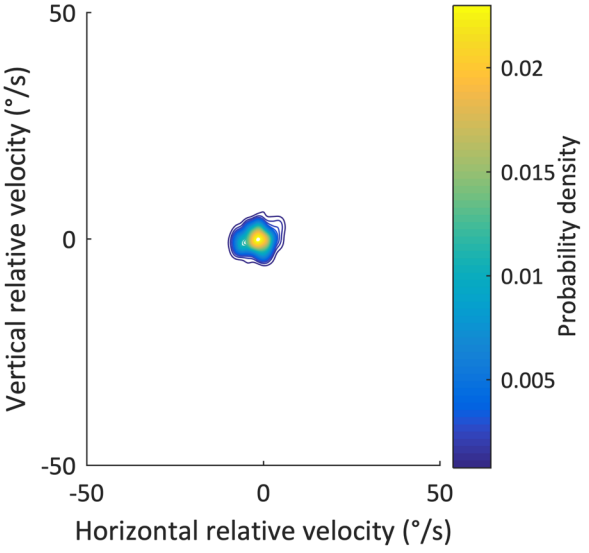

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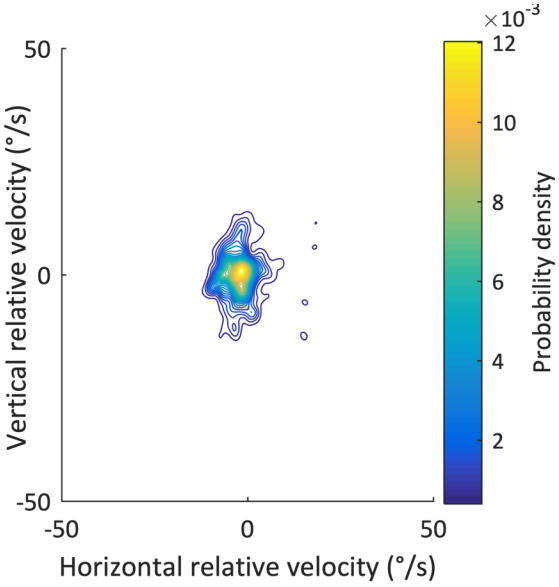

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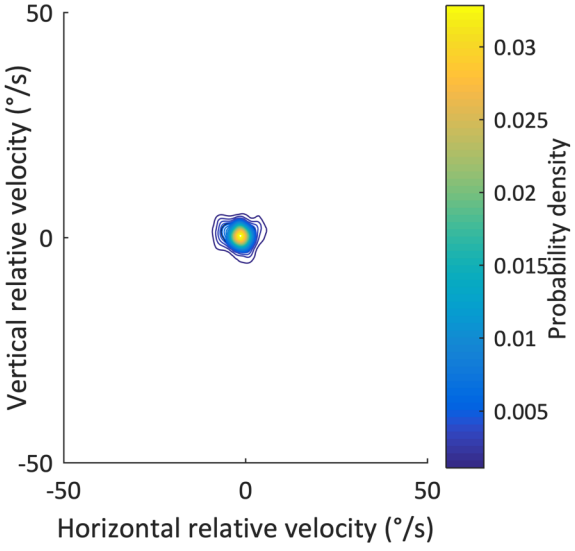

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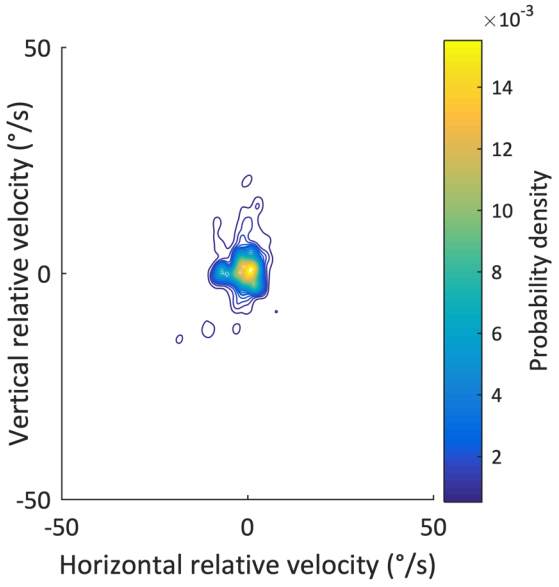

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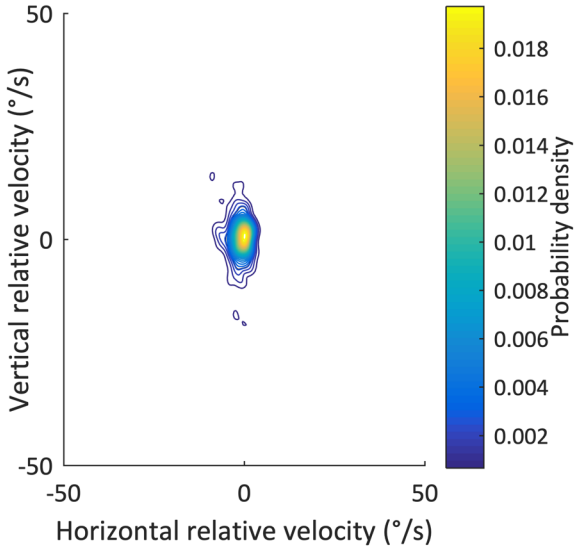

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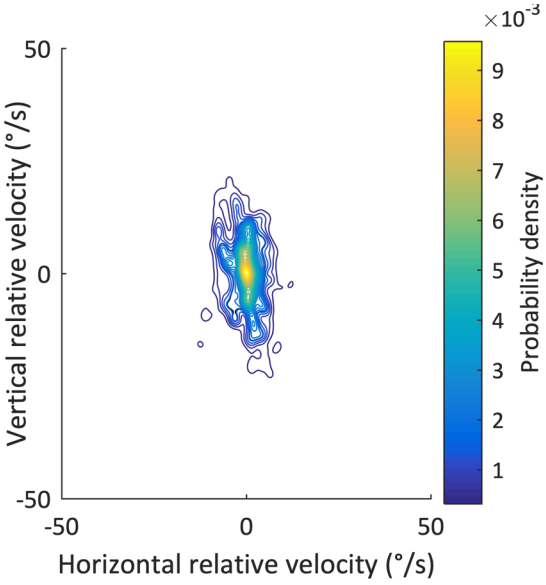

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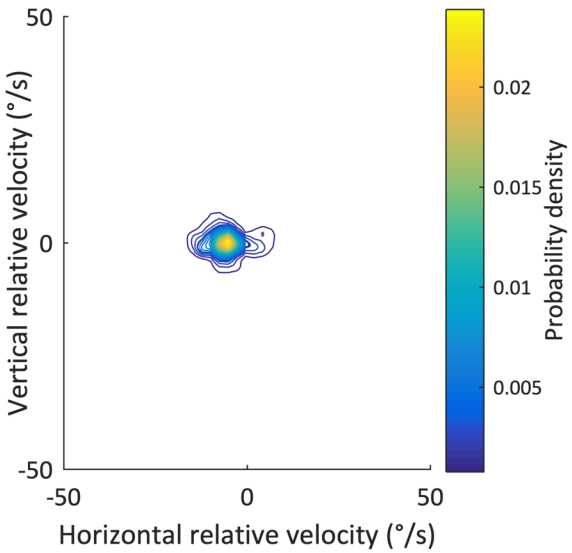

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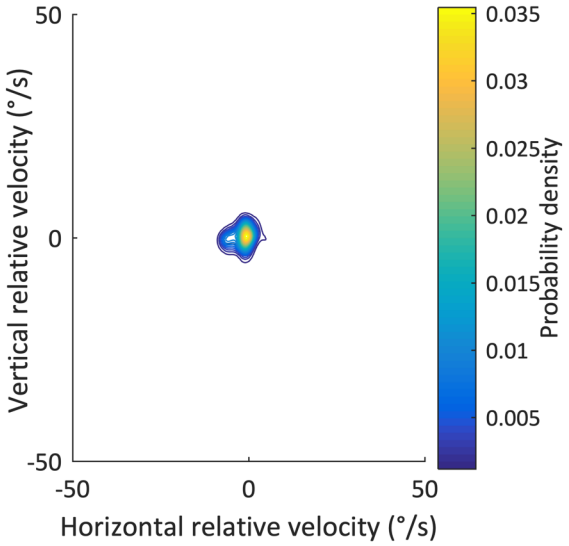

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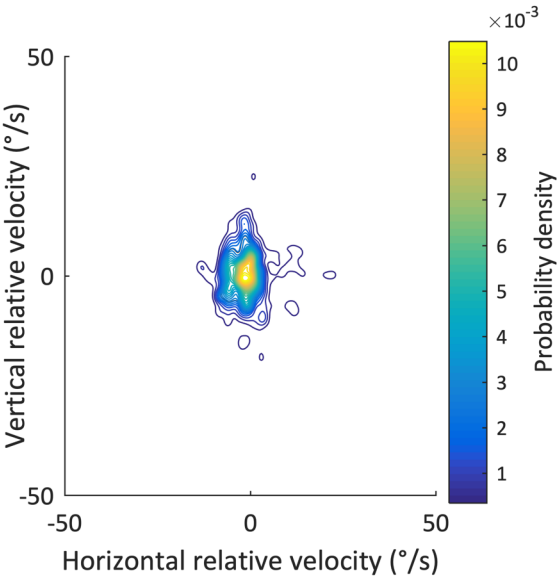

Appendix S: List of presentations, posters and publications arising from the research

Publications

Zahidi AA, Vinuella-Navarro V, and Woodhouse JM. 2018. Different visual development: norms for visual acuity in children with Down's syndrome. Clinical and Experimental Optometry. 101: 535–540

Zahidi AA, Woodhouse JM, Erichsen JT, and Dunn MJ. 2017. Infantile nystagmus: An optometrist's perspective. Clinical Optometry 2017:9 123–131

Oral presentation

Zahidi AA, Woodhouse JM, Erichsen JT, McIlreavy L. 2017. Visual profile of children with Down's syndrome and Nystagmus: A retrospective study. British Congress Of Optometry and Vision Science (BCOVS) 2017, Plymouth, 4-5 September 2017

Poster Presentation

Zahidi AA, McIlreavy L, Erichsen JT, Woodhouse JM. 2018. Development of visual acuity and refractive error in children with Down's syndrome and vystagmus. American Academy of Optometry meeting, Academy 2018, San Antonio, Texas, US, 7-10 November 2018

Zahidi AA, Woodhouse JM, Erichsen JT, McIlreavy L. 2017. Visual profile of children with Down's syndrome and Nystagmus: A retrospective study. Children's Vision Research Society (CVRS) Conference, Coleraine, Northern Ireland, UK, 15-18 June 2017

Zahidi AA, Woodhouse JM, Erichsen JT. 2016.The effect of stimulus type and size on the quality eye movement data in patients with nystagmus. Optometry and Vision Science Congress, Rome, Italy, October 20-22, 2016