The Impact of Stress on Visual Function in Nystagmus

A thesis submitted to Cardiff University for the degree of

Doctor of Philosophy

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This work has not previously been accepted in substance for any degree and is not concurrently submitted in candidature for any degree.

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Abbreviations

2AFC	–	Two alternative forced choice
AA	–	Anticipatory anxiety
AHP	–	Abnormal head posture
Alt	–	Alternating
ANOVA	–	Analysis of variance
AOS	–	Accessory optic system
AP	–	Asymmetric pendular
AMD	–	Age related macular degeneration
BDJ	–	Bidirectional jerk
BLO	–	Baseline oscillation
CEMAS	–	Classification of eye movement abnormalities and strabismus
CC	–	Landolt C control
Cd	–	Candelas
c/deg	–	Cycles per degree
CI	–	Confidence interval
CN	–	Landolt C nystagmus
CRT	–	Cathode ray tube
CS	–	Contrast sensitivity
CSF	–	Contrast sensitivity function
D	–	Dioptre
dB	–	Decibel
DC	–	Dioptre cylinder
DJ	–	Dual jerk
DLPN	–	Dorsolateral pontine nucleus
DS	–	Dioptre sphere
DVA	–	Dynamic visual acuity
DVN	–	Dorsal vestibular nucleus
EBNs	–	Excitatory burst neurons
EC	–	Tumbling E control
EN	–	Tumbling E nystagmus
EOG	–	Electro Oculography
EOMs	–	Extraocular muscles
ET	–	Esotropia
FACT	–	Functional acuity contrast test
FEF	–	Frontal eye fields
FMNS	–	Fusional maldevelopment nystagmus syndrome
FRMD7	–	FERM domain-containing 7
GABA	–	Gamma amino butyric acid
GC	–	Gratings control
GN	–	Gratings nystagmus
Hyperp	–	Hyperphoria
Hz	–	Hertz
IAPS	–	International affective picture system
IBNs	–	Inhibitory burst neurons

INS	–	Infantile nystagmus syndrome
IOP	–	Intraocular pressure
IPS	–	Intermittent photic stimulation
IR	–	Infra red
J	–	Jerk
JL	–	Jerk left
JL_{EF}	–	Jerk left with extended foveation
JR	–	Jerk right
JR_{EF}	–	Jerk right with extended foveation
kHz	–	Kilohertz
L	–	Left
LEDs	–	Light emitting diodes
LGN	–	Lateral geniculate nucleus
LN	–	Latent nystagmus
LVN	–	Lateral vestibular nucleus
µMho	–	Microsiemens
m	–	Metres
mA	–	Milliamp
MAR	–	Minimum angle of resolution
MAS	–	Manifest anxiety scale
MLF	–	Medial longitudinal fasciculus
MLN	–	Manifest latent nystagmus
mm	–	Millimetres
ms	–	Milliseconds
MST	–	Middle superior temporal area
MT	–	Middle temporal cortex
MVN	–	Medial vestibular nucleus
nIII	–	Third motor nucleus (oculomotor)
nIV	–	Fourth motor nucleus (Trochlear)
nVI	–	Sixth motor nucleus (Abducens)
NAF	–	Nystagmus acuity function
NAFP	–	Nystagmus acuity function of position
NAFX	–	Expanded nystagmus acuity function
NEI	–	National eye institute
NEI-VFQ	–	National eye institute visual function questionnaire
NN	–	Nystagmus network
OCT	–	Optical coherence tomography
OKN	–	Optokinetic nystagmus
Ortho	–	Orthophoric
P	–	Pendular
PAN	–	Periodic alternating nystagmus
PC	–	Pseudo cycloid
PFS	–	Pendular with foveating saccades
PJ	–	Pseudo jerk
PP	–	Pseudo pendular
PPFS	–	Pseudo pendular with foveating saccades
PPRF	–	Paramedian pontine reticulate formation

R	–	Right
R1	–	First relaxed period
R2	–	Second relaxed period
R3	–	Third relaxed period
RGCs	–	Retinal ganglion cells
riMLF	–	Rostral interstitial nucleus of the medial longitudinal fasciculus
RT	–	Response time
R.U.N.	–	Research unit for nystagmus
s	–	Seconds
SC	–	Superior colliculus
SD	–	Standard deviation
SD-OCT	–	Spectral domain optical coherence tomography
SDp	–	Standard deviation of eye position
SDv	–	Standard deviation of eye velocity
SF	–	Social function
SkC	–	Skin conductance
SOA	–	Supra-oculomotor area
SSC	–	Scleral search coil
STAI	–	State and trait anxiety inventory
T	–	Triangular
TD	–	Task demand
TENS	–	Trans-cutaneous electrical nerve stimulation
Tf	–	Length of foveation per second
TT	–	Threshold testing
UDTR	–	Up-down transformed response
µV	–	Microvolt
V1	–	Visual area 1
V2	–	Visual area 2
V3	–	Visual area 3
V5	–	Visual area 5
VA	–	Visual Acuity
VAS	–	Visual analogue scale
VDU	–	Visual display unit
VOR	–	Vestibular ocular reflex
XT	–	Exotropia

Abstract

Infantile Nystagmus Syndrome (INS) is defined as a constant involuntary movement of the eyes, affecting 0.12% of the population. Previous research shows that eye movements in patients with nystagmus increase in stressful conditions, and they report that their vision gets worse. However, there have been no definitive conclusions as to the effect of stress on visual acuity (VA).

The aim of the studies described here was to assess visual function, including VA, during periods of stress.

The results showed that there was no difference in VA measured with horizontally and vertically oriented Landolt C's, but, in agreement with published research, VA was found to be poorer when using vertically oriented gratings as compared to horizontal gratings. Using a Trans-Cutaneous Electrical Nerve Stimulation (TENS) machine, an effective clinical stressor, we confirmed that the intensity of nystagmus increased when under stress; however VA, as measured using Landolt Cs, was not affected. Patient response time also increased during stressful periods and was significantly longer in INS than in control subjects.

Using a questionnaire, we identified the most stressful situations for patients with nystagmus as being: "finding a person in a crowd" and "crossing a road in heavy traffic". Under stress, rather than vision becoming blurred, patients with nystagmus reported that they "take longer to see things" and "have difficulty with seeing facial features and small detail".

The results reported here have important implications for patients with nystagmus in the real world, strongly suggesting that, although maximum acuity is unaffected by stress, more time should be allowed for tasks at both work and school. Further research is required to fully understand the changes in other aspects of visual function with stress.

“I’ve found it has little to do with the things you see and everything to do with the way you see them”

Elliott Erwitt (1928 -)

Chapter 1: Eye Movements

1.1 General Introduction

Nystagmus is defined as constant involuntary movement of the eyes. These movements are generally in the horizontal plane, although some vertical and rotatory movement can sometimes be seen (Abadi and Kingsmith 1979). Anecdotal evidence exists to suggest that nystagmus is worsened by stressful conditions. Until very recently the only evidence to support this was observations of the opposite effect, i.e. when subjects relaxed, their eye movements were not as marked (Abadi and Dickinson 1986). Recent investigations have shown that stress does in fact cause a worsening of eye movements (Cham et al. 2008a). However, none of these previous studies have been able to draw conclusions regarding the effect of stress on visual acuity (VA). The main aim of the studies described here is to investigate the effects of stress on the visual function of people with nystagmus.

Since nystagmus is an eye movement disorder, we must first understand the way in which the eyes move under normal conditions. The purpose of the present chapter is to outline normal eye movements and their function in everyday life.

1.2 Brief Description of the Visual System

The visual system is a highly complex neural pathway that begins by translating light energy into nervous impulses. Light is firstly focussed onto the light-sensitive retina which is made up of layers of neural cells (Figure 1.1).

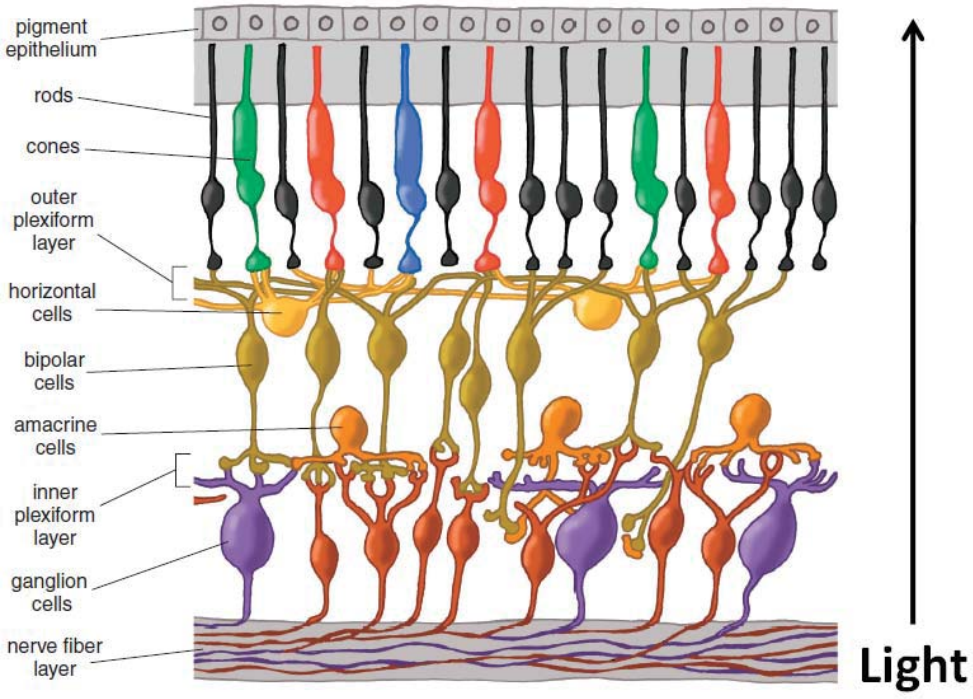

Figure 1.1: Diagram of the layers of the retina (Adapted from Kolb 2003).

As well as the divisions made with regard to the layers of the retina, a further topographical division can be made into central (macular ≈ 6mm diameter at the centre of retina; fovea ≈ 1.5mm diameter at the centre of the macular (Forrester et al. 2006)) and peripheral regions of the retina. There are two types of photoreceptor in the retina: rods and cones. The cone cells are more densely situated in the central retina, with a peak density of 199,000/mm^2 over an area around 0.2°, this number almost halving just 150µm away from the foveal centre (Curcio et al. 1990). At the foveola (0.35mm diameter area at the centre of the fovea (Forrester et al. 2006)) the cone photoreceptors have a one-to-one relationship with the retinal ganglion cells (RGCs), enabling them to resolve exquisite detail (Remington 1998). The rod photoreceptors are absent from the centre of the fovea and appear at around 100µm from the foveal centre (Curcio et al. 1990). The peak density of rods (176,000/mm^2) is found in a ring surrounding the fovea, around 3-5mm from the centre (Curcio et al. 1990). Rod and cone photoreceptors are also sensitive to different luminance levels. The rod photoreceptors are active under low light (scotopic) conditions, and their

sensitivity peaks at a wavelength of 507nm (Schwartz 1999). The cone photoreceptors are active at higher (photopic) levels of illumination, and there are three different types, each containing a specific photopigment that is sensitive to long (565nm), medium (535nm) and short (430nm) wavelength light (Schwartz 1999), providing the basis for colour vision.

1.2.1 The Primary Visual Pathway

Signals originating in the neural retina leave the eye via the axons of the ganglion cells, which having exited the eye, form the optic nerve. The nerve continues to carry the signal to the optic chiasm (Figure 1.2), where only the nasal retinal fibres from each eye cross over. It is this cross over which results in the left cortex receiving information only from the right visual field, and the right cortex receiving information only from the left visual field. Dorsal to the optic chiasm, the pathway is referred to as the optic tract, which relays the neural signals to the Lateral Geniculate Nucleus (LGN) of the thalamus (Figure 1.2).

The LGN has six layers; layers one and two are the magnocellular layers, receiving information from the magnocellular ganglion cells. These layers of the LGN are associated with motion perception (Lee et al. 1979; Hutchins and Corbett 1996). Layers three to six are the parvocellular layers that receive information from the parvocellular ganglion cells and are associated with colour and high contrast resolution (Wiesel and Hubel 1966; Hutchins and Corbett 1996; Remington 1998; Schneider et al. 2004).

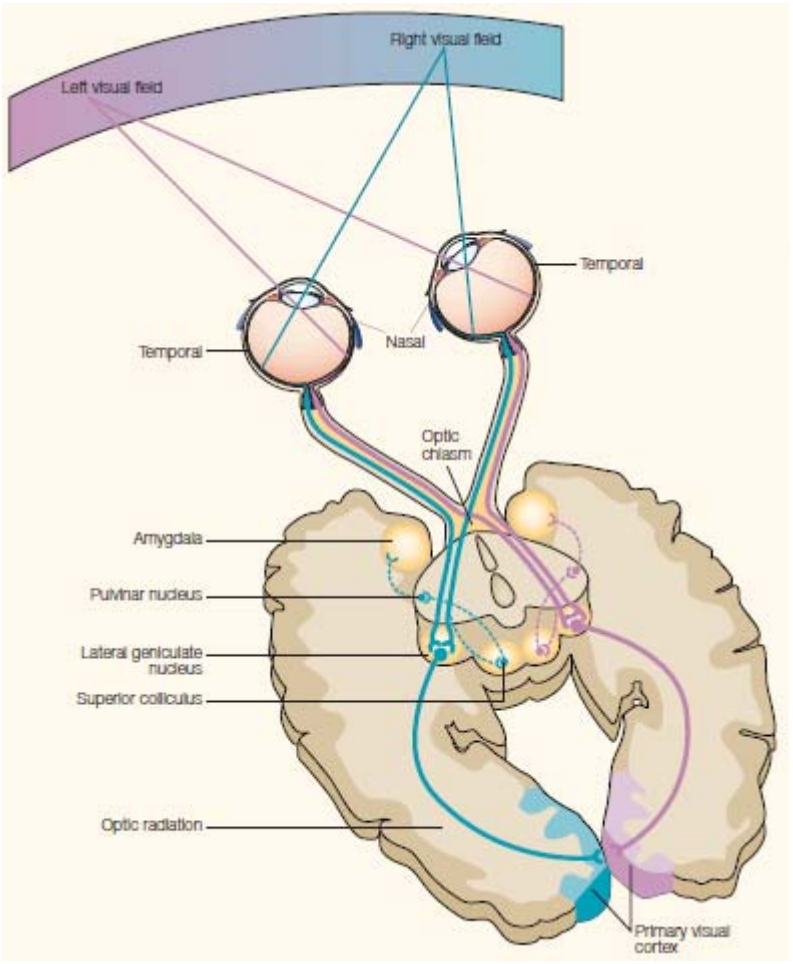

Figure 1.2: Diagram of the visual pathways (Hannula et al. 2005)

The axons transporting the visual signal to the primary visual cortex (V1) originate from LGN cells and emerge to form the optic radiations. From V1, the pathways project on to 24 further cortical centres that maintain the topographical representation of visual space. Following area V1, these further projections pass through visual areas 2 (V2) and 3 (V3), but after V3, the projections can be split into two distinct streams: dorsal and ventral (Bear et al. 2007b). The ventral (or "what") stream, carrying parvo information, is involved in the recognition of objects. The dorsal (or "where") stream, carrying magno information, is involved in the perception of location and motion (Schwartz 1999). In the case of eye movements, the most important of these is the dorsal stream because of its function in the detection of motion and in identifying the position of objects in the visual field. The first

cortical area of the dorsal stream is visual area 5 (V5) (or middle temporal cortex–MT) (Schwartz 1999). Most of the cells in V5 are specifically sensitive to motion. In a further area (middle superior temporal–MST), cells are sensitive to more specific types of motion (e.g. radial and circular) (Bear et al. 2007b).

1.2.2 The Accessory Optic System

Another important parallel visual system involves retinal projections to the accessory optic system (AOS). This consists of the optic tract nucleus, and the medial, lateral and dorsal accessory nuclei (Simpson 1984; May and Corbett 1996). Some of the magnocellular retinal ganglion cells leave the optic tract before the LGN and terminate in these nuclei (Simpson 1984; May and Corbett 1996). Neurons of the accessory nuclei are sensitive to movement of large areas of the visual field and transmit information about both speed and direction (Simpson et al. 1979). The optimal directional sensitivity is different for each of the accessory nuclei (medial and lateral being sensitive to vertical movement and dorsal sensitive to horizontal movement), and the optimal speed of movement ranges from 0.5 to 10°/s (Simpson et al. 1979; Simpson 1984). The AOS is involved in signalling self-motion and is complementary to the vestibular system (Simpson et al. 1979). The accessory nuclei project (indirectly) to the oculomotor, abducens and trochlear nuclei and are responsible for stabilising eye movements, namely Optokinetic Nystagmus (OKN) (see section 1.7.2).

1.2.3 The Retinocollicular Pathway

One of the most important areas involved in the control of eye movements is the superior colliculus (SC), located in the dorsal midbrain. The pathway is known as the retinocollicular pathway and is involved in visual attention (Schneider 1969; cited in Cowey and Perry 1980).

The retinocollicular pathway means that the SC receives input from the retina, 10% of ganglion cells having a direct projection here (Bear et al. 2007b). The SC has connections to many different areas of the brain and is heavily involved in efference copy (oculomotor feedback) (Sommer and Wurtz 2008). The SC can be divided into two laminar zones: superficial and deep (Lund 1972). The superficial zone of the SC receives direct input from the retina (retinocollicular pathway – section 1.2.3) as well as from the deep layers of the visual cortex, and projects to the deep zone of the SC, as well as to the dorsal LGN (Lund 1972). The deep zone receives input from the auditory areas of the brain, as well as cortical areas other than the visual cortex. These deeper layers project to the brainstem and to areas involved in eye movement (vertical and horizontal gaze centres) and head movement (Lund 1972; May and Corbett 1996; Waitzman et al. 2002). The many inputs received by SC allow it to construct a topographic "map" of the world. Once a stimulus has been detected, information regarding its location on the retina is transmitted to the oculomotor areas that are involved in saccades (section 1.5.1) (Cowey and Perry 1980; Waitzman et al. 2002; Bear et al. 2007a). Although this pathway is primarily involved in the location of objects in the peripheral field, foveal representation has also been found in the SC (Cowey and Perry 1980).

1.3 The Extraocular Muscles (EOMs)

Six muscles control the movements of each eye, the medial and lateral recti, the superior and inferior recti, and the superior and inferior oblique muscles (Remington 1998). Like skeletal muscle, the extra ocular muscles (EOMs) are striated but have a more delicate connective tissue layer, which has many nerve and elastic fibres. Extra ocular muscles are

also much more vascular than normal skeletal muscle (Remington 1998). The muscles attach to the sclera, as shown in figure 1.3.

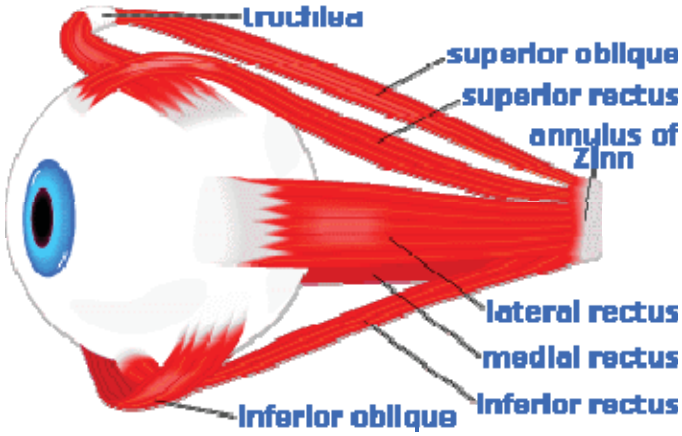

Figure 1.3: Diagram of the muscle insertions of the left eye (Montgomery 2011)

When the eyes make a conjugate binocular movement, the muscles in each eye must obey two laws. Herring's law states that the yoked (agonist) muscles of both eyes (i.e. the muscles that pull the two eyes in the same direction) must receive equal stimulation at the same time. Sherrington's law states that the antagonistic muscles in one eye must receive equal but opposite innervations (Remington 1998). These laws are important in eye movements and enable the tracking of moving objects, or the moving of gaze from one position to another whilst maintaining conjugate binocular vision. Horizontal eye movements are controlled by the medial and lateral recti of each eye. Vertical movements are more complicated, as these are controlled by a combination of interactions of the superior and inferior recti, as well as the superior and inferior oblique muscles.

The six muscles of each eye are innervated by the third, fourth and sixth cranial nerves. The lateral rectus muscle is controlled by the sixth nerve, the superior oblique muscle is controlled by the fourth nerve, and the medial, superior and inferior recti, as well as the inferior oblique muscles, are controlled by the third nerve (Remington 1998).

The EOMs are innervated by means of three receptor types: muscle spindles, palisade endings and Golgi tendon organs (Buttner-Ennever et al. 2006; Weir 2006). The muscle spindles found in the EOMs are as numerous as those found in skeletal muscle used for fine control, such as in the hand (Lukas et al. 1994). The palisade endings are found exclusively in the tendinous attachments of the EOMs to the globe (Richmond et al. 1984; Eberhorn et al. 2005; Buttner-Ennever et al. 2006). Two recent studies have traced the origin of the cell bodies associated with the palisade endings and found them to be in close proximity to the oculomotor nuclei (Lienbacher et al. 2011; Zimmermann et al. 2011). As yet, the exact function of the palisade endings is unknown (Eberhorn et al. 2005; Buttner-Ennever et al. 2006; Lienbacher et al. 2011), although Lienbacher et al. (2011) suggest that they may have both motor and sensory purposes. In contradiction, Zimmermann et al. (2011) report findings that indicate motor rather than sensory features. Muscle spindles, palisade endings and golgi tendon organs are thought to have a possible role in proprioception.

1.3.1 Efference Copy and Proprioception

Once the eyes have been moved to a new position by the EOM's, it is important that the brain knows where the eyes are in order to keep them in that position, orientate the body, or control gaze shifts to a new position. This is achieved by efference copy and proprioception. Efference copy is the feedback to other brain centres of the motor innervations sent to the EOMs (Bridgeman and Stark 1991) and provides a signal that indicates where the eyes are expected to be in the orbit rather than information on where the eyes actually are (Bridgeman 1995). By the comparison of the visual signals from the retina with the motor signals sent to the EOMs (Carpenter 1988b), efference copy also allows unambiguous differentiation between perceived motion from retinal image slip of

the object caused by eye movement and actual movement of the object itself. Efference copy is present in almost all eye movements, with the exception of the slow phases of the vestibular ocular reflex (VOR) and OKN (Bridgeman 1995).

Proprioception provides a much smaller feedback of current eye position and demonstrates only a small change in signal for even large eye movements (Bridgeman and Stark 1991). It is even doubtful whether proprioception has any role in maintaining a stable view of the world (Wurtz 2008). However, proprioception has links to the SC, visual cortex, cerebellum and nucleus prepositus (Bridgeman and Stark 1991; Buttner-Ennever et al. 2006). Buttner-Ennever et al. (2006) put forward a possible neural pathway for proprioception with an emphasis on the palisade endings, suggesting that signals are sent from the palisade endings to the spinal trigeminal nucleus, which in turn projects to the cerebellum and SC. Nevertheless Carpenter (1988b) indicates that efference copy is the most useful form of feedback for eye position, and this view is supported by many other subsequent publications (Bridgeman and Stark 1991; Buttner-Ennever et al. 2006; Wurtz 2008).

1.4 The Role of Eye Movements in Normal Vision

When observed individually, eye movements can be considered to involve rotation about one or more axes i.e. horizontal, vertical and torsional (Figure 1.4).

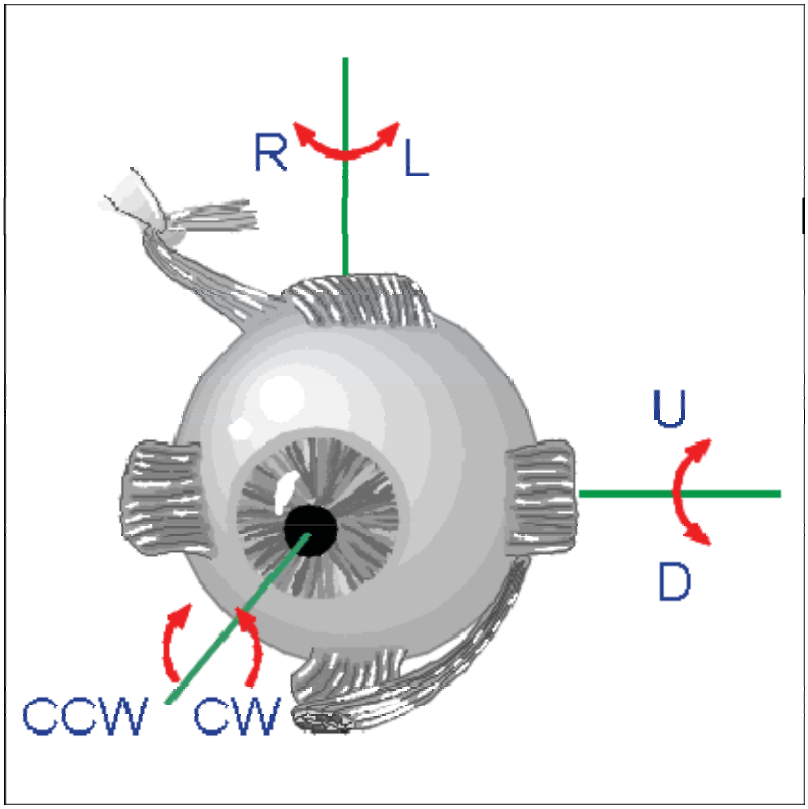

Figure 1.4: Diagram of the axes of movement (Vilis and Tweed 1996)

Horizontally, the movements are adduction and abduction, movement of the eyes toward and away from the nose, respectively. Vertically, the movements are elevation and depression. Binocular eye movements are termed either version or vergence movements. A version movement is the term used to describe those movements in which both eyes move in the same direction (conjugately). Vergence movements are those in which the eyes move in opposite directions, e.g. convergence whilst viewing near tasks (Rashbass and Westheimer 1961; Leigh and Zee 1999; Masson et al. 2002).

1.4.1 Why do we Need Eye Movements?

Eye movements can essentially be split into two classes: fixation/gaze shifting and gaze stabilising eye movements (Leigh and Zee 1999). The fixational/gaze shifting eye movements are those involved in locating an object in space or tracking moving objects. The eyes are

moved in order to place the image of the object onto both foveae. Once the image is placed on the fovea, it must then be kept there. If the object moves, then other fixational eye movements are employed. However, during self locomotion, stabilising eye movements are used. There are a number of different eye movements within the categories of fixational/shifting and stabilising movements. These movements and their neural pathways will be described in sections 1.5 and 1.7.

The positioning of the images of objects of regard on the fovea and the maintenance of this fixation are extremely important. For most detailed vision, the object being viewed needs to be kept within 0.5° of fixation (Saunders 1973; Jacobs 1979; Leigh and Zee 1999). If the object of regard is not held on the fovea by gaze stabilising eye movements, the image of the object of regard may "slip" across the retina. A small amount of retinal slip can be dealt with by the visual system. In fact, very small eye movements exist to prevent a perfectly still image on the retina (microsaccades) (Carpenter 1988c; Leigh and Zee 1999). Westheimer and McKee (1975) showed no change in VA for Landolt C's moving across the fovea at up to 2.5°/s. Stereopsis has also been shown to be unaffected by retinal image motions of up to 2°/s (Westheimer and McKee 1978). The degree to which VA is affected by retinal slip is dependent on the spatial frequency of the target (Burr and Ross 1982). Burr and Ross (1982) showed that a small degree of retinal image motion can, in fact, improve contrast sensitivity. They demonstrated that, if moved at the correct velocity, images that would only be seen at high contrast when stationary are visible at lower contrast. They further found that retinal image motion has a deleterious effect on the perception of high spatial frequencies but enhanced the detection of low spatial frequencies. Leigh and Zee (1999) state that, for high spatial frequency targets such as optotypes used in VA measurement,

retinal image motion must be kept below 5°/s. Although above this speed visual acuity is worsened (Burr and Ross 1982; Leigh and Zee 1999), at an image motion of 5°/s or less, visual acuity remains maximal. These findings highlight the low tolerance for image motion/slip and the importance of the gaze stabilising movements in the optimal processing of the image on the retina, as well as that of gaze shifting eye movements in the initial placement of the image accurately at the fovea.

1.5 Fixational Eye Movements

The first class of eye movements that we will discuss includes those which move the eyes to fixate an object of interest within the visual field. These are known as the fixational, targeting or gaze shifting eye movements (Dodge 1903; Carpenter 1988c; Leigh and Zee 1999). Within this category, there are three types of eye movement: saccades, smooth pursuit and vergence (Dodge 1903; Leigh and Zee 1999).

1.5.1 Saccades

Saccades are rapid eye movements used to move fixation from one object of interest to another. Saccades can be further divided; the main types are summarised in Table 1.1. Saccades are the fastest of all the eye movements. Moreover, it is well documented that, the larger the amplitude, the faster the speed of the movement and the longer the duration of the saccade (Dodge 1903; Bahill et al. 1975b). Large amplitude saccades (≥30°) can reach up to 700°/s (Boghen et al. 1974; Carpenter 1988c), although Bahill et al. (1975a) indicate that 86% of saccades made in day to day life do not exceed 15°. The peak velocity and duration of saccades are tightly linked to its amplitude, larger amplitude saccades having a longer duration and higher peak velocity. This relationship is known as the “main sequence”

(Figure 1.5) (Bahill et al. 1975b; Harwood et al. 1999; Leigh and Zee 1999). Saccades have a latency of approximately 200ms (Gaymard and Pierrot-Deseilligny 1999; Orban de Xivry and Lefevre 2007). When making saccades, subjects do not see the world as rushing past because visual perception, specifically that of lower spatial frequencies, is suppressed. This is known as saccadic suppression. Because it is responsible for motion detection, the magnocellular pathway appears to be selectively suppressed (Leigh and Zee 1999). In order to make a saccade and then keep the eyes in that position, the system employs a particular direction specific neural gaze shifting pathway. Horizontal movements are mediated by the paramedian pontine reticulate formation (PPRF), and vertical movements are mediated by the rostral interstitial nucleus of the medial longitudinal fasciculus (riMLF) in the midbrain (Carpenter 1988a; May and Corbett 1996; Leigh and Zee 1999).

Classification		Definition
Volitional Saccades	**General**	A saccade generated by a conscious decision to do so.
	Predictive/Anticipatory	Saccades made to a particular location when a stimulus is predicted or anticipated to appear in this area.
	Memory-guided	Saccades made to an area of the visual field where a stimulus was previously presented.
	Antisaccades	Saccades made in the opposite direction to a stimulus (when subjects are asked to do so).
	To Command	Saccades made when told to do so.
Reflexive Saccades	Saccades made in response to stimuli in a particular area of the field. (Stimulus can be visual, auditory or tactile.)	
Quick Phases	These are the quick phases of Vestibular or Optokinetic Nystagmus, or the resetting movements seen in nystagmus.	

Table 1.1: The classification of the main types of saccadic eye movements (adapted from Leigh and Zee 1999)

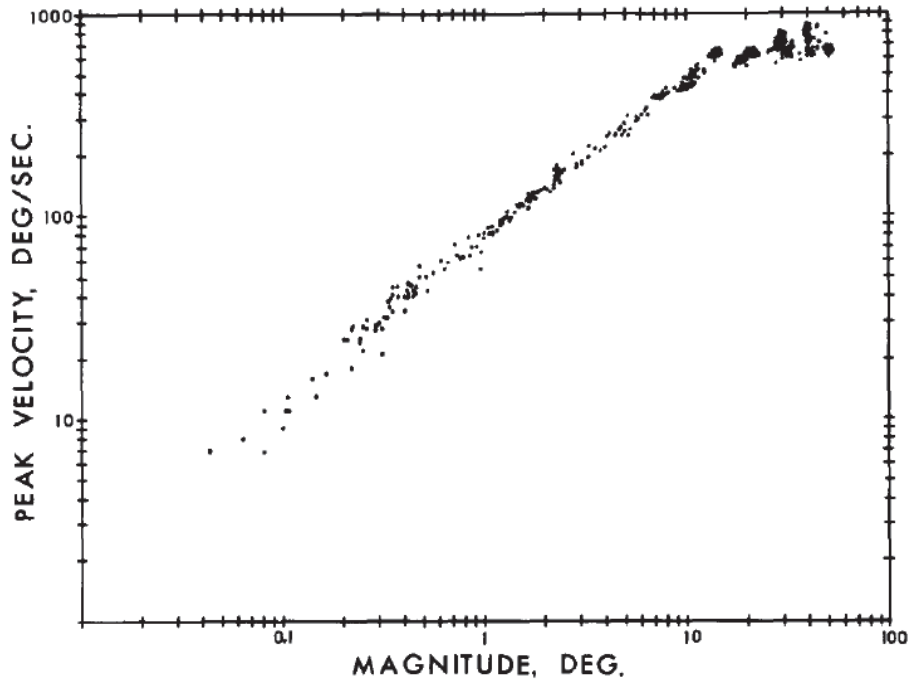

Figure 1.5: Main sequence relationship between saccadic amplitude and peak velocity (Bahill et al. 1975b).

For simplicity we will look at a horizontal saccade to the left in response to a stimulus in the left visual field. The PPRF receives signals from both the right frontal eye fields (FEF) and the SC, i.e. provoked by a stimulus in the left visual field. These inputs contain information on the size and direction of the saccade required (Gaymard and Pierrot-Deseilligny 1999; Orban de Xivry and Lefevre 2007). The stimulus in our example would be detected in the right hemisphere of the brain, and so the FEF would project to the contralateral (left) PPRF. The PPRF then sends signals using the excitatory burst neurons (EBNs) and inhibitory burst neurons (IBNs) to the extra ocular muscles. The EBNs contain the signal for the phasic pulse of innervation (May and Corbett 1996). Again for simplicity, we will look at the path of the EBNs. The PPRF sends signals via the EBNs to the ipsilateral abducens (sixth) motor nucleus (nVI) from where the signal then passes down the abducens nerve (cranial nerve VI) to the lateral rectus of the left eye. Another signal also passes via the abducens interneurons, which project along the medial longitudinal fasciculus (MLF) to the contralateral oculomotor (third) nucleus (nIII) from where the impulses pass via the oculomotor nerve (cranial nerve

III) to the medial rectus of the right eye (May and Corbett 1996; Leigh and Zee 1999; Longstaff 2005b). This pathway is shown diagrammatically in figure 1.6. Once the eyes have made the saccade, they need to remain in this position, and this is accomplished by the tonic step of innervation that is controlled by the horizontal neural integrator (Leigh and Zee 1999). The neural integrator will be discussed in more detail in section 1.6.

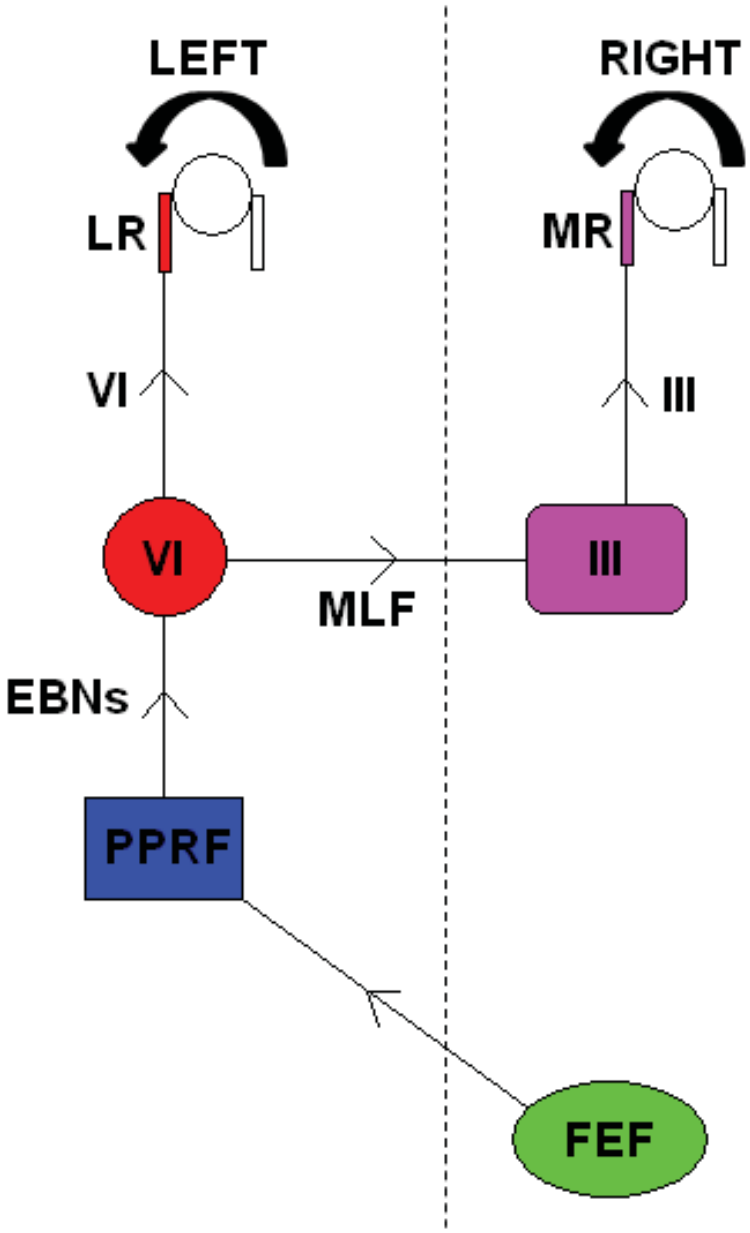

Figure 1.6: Diagrammatic representation of the neural pathway of a leftward saccade. FEF - Frontal eye field, PPRF - Paramedian pontine reticulate formation, EBNs - Excitatory burst neurons, VI - Abducens nucleus and nerve, III - Oculomotor nucleus and nerve, MR - Medial rectus, LR - Lateral rectus, MLF - Medial longitudinal fasciculus

1.5.2 Smooth Pursuit

Smooth pursuit eye movements are those used to keep the image of a relatively small object of regard on the fovea as it crosses the visual field. They are defined by Dodge (1903) as being "those eye movements in which the line of regard follows an object moving across the field of vision". Smooth pursuit movements can follow objects moving in the visual field at speeds of up to 100°/sec. (May and Corbett 1996). However, there is a slight delay of approximately 100ms before pursuit movements begin (Leigh and Zee 1999).

The speed and location of the target are analysed by the lateral, parietal and midtemporal cortices (May and Corbett 1996; Longstaff 2005b; Hutton and Weekes 2007). These areas transmit signals to the cerebellum, specifically the flocculus and paraflocculus in the vestibular nucleus of the cerebellum, via the dorsolateral pontine nucleus (DLPN) (May and Corbett 1996), the paraflocculus being more important for the control of smooth pursuit movements (Leigh and Zee 1999). Pre-motor neurons project from this area to nIII, nIV (Trochlear [fourth] motor nucleus) and nVI to elicit the necessary eye movements (May and Corbett 1996; Leigh and Zee 1999; Longstaff 2005b). Unlike the pulse and step of saccadic eye movements, smooth pursuit requires a variable response, which allows for the gradual change in fixation, without producing a jerky movement (May and Corbett 1996; Leigh and Zee 1999).

1.5.3 Vergence

Vergence movements are those observed when a subject tries to maintain the image of an object on the fovea as it moves closer or farther away. These are also the only non-conjugate eye movements (Longstaff 2005b). Vergence is seen as being similar to saccades

in that it is a response to stimuli eccentric to the fovea; in this case, the images would be at disparate points on the retina (Dodge 1903). However, vergence can also be triggered by a blurred retinal image, caused by a change in the proximity of the target. As a result of this, vergence is also linked to accommodation of the lens and miosis of the pupil in what is known as the near triad (Remington 1998). Signals initiating the vergence response are found in areas adjacent to the frontal eye fields. These send signals to the supra-oculomotor area (SOA), which then further projects to nVI and nIII (May and Corbett 1996; Gamlin 2002). These neurons also send signals to the Edinger-Westphal nuclei which control both accommodation and miosis (May and Corbett 1996; Remington 1998; Gamlin 2002).

1.6 The Neural Integrator

As mentioned in section 1.5.1, the neural integrator is responsible for holding gaze in eccentric positions. Normal subjects are able to hold their eyes in eccentric gaze, even in the dark. This suggests that more than visual cues are used (Becker and Klein 1973). It is necessary to have the neural integrator, as the eye is under elastic restoring forces when in eccentric gaze that would otherwise force it to return to the primary position (Bockisch and Hegemann 2008). There are two types of innervations occurring to keep the eyes in eccentric gaze. The pulse innervation, which is a velocity command (the neural signal codes for the velocity needed to move the eye to a given position), overcomes the viscosity of the orbital contents to move the eye into its eccentric position. The step innervations, which are position commands, maintain contraction of the relevant extra ocular muscles to keep the eye steady in this position (Leigh and Zee 1999). The neural integrator uses the velocity command for the initial pulse of innervation to produce the relevant step innervations (Goldman et al. 2002; Crawford et al. 2003). The neural integrator is based upon

communication between the cerebellum and brain stem. The cerebellum receives inputs from the paramedian tracts and then projects to the flocculus and paraflocculus, as in smooth pursuit. This same pathway also provides an efference copy of eye position used in gaze control (Leigh and Zee 1999). As with the various other types of eye movements, different centres of the brain are used for vertical and horizontal gaze holding. For vertical holding, the midbrain interstitial nucleus of Cajal is the most important area (Buttner et al. 2002). Horizontal holding incorporates two areas, these being the pontine nucleus prepositus hypoglossi and the medial vestibular nucleus (Goldman et al. 2002).

If the neural integrator works perfectly, then the eyes move to their eccentric position and are held there (Figure 1.7A). However, sometimes the neural integrator is termed "leaky". This is seen as the eyes drifting from eccentric gaze back to the primary position, pulled by the elastic restoring forces. These drifts follow an exponential pattern (Leigh and Zee 1999), which is demonstrated in figure 1.7B.

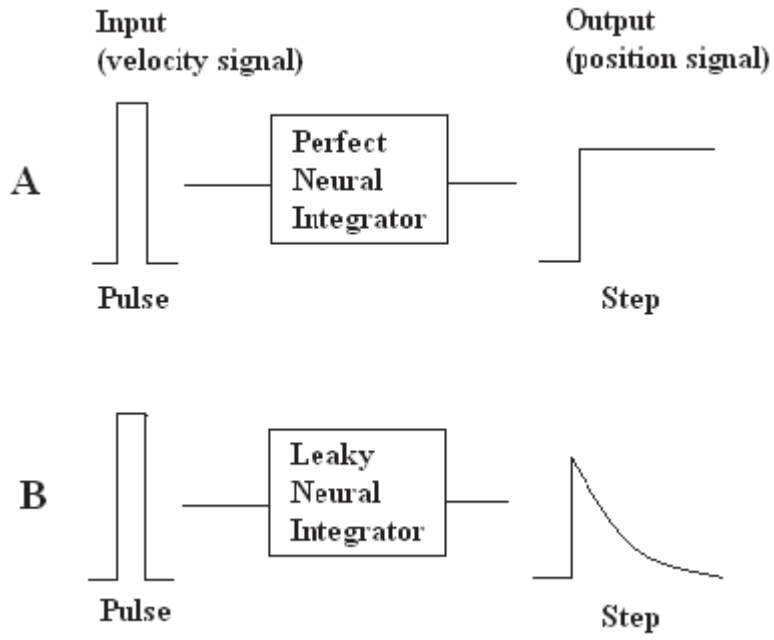

Figure 1.7: A) Perfect neural integrator B) Leaky neural integrator (adapted from Leigh and Zee 1999)

A drift of this type requires another pulse of innervation to make a saccadic (jerk) movement moving the eyes back to their correct eccentric position (Abel et al. 1978a). The principle of a "leaky" neural integrator is considered a possible underlying mechanism in the case of end-point or gaze evoked nystagmus, in which a drift from fixation is followed by a corrective jerk movement (Abel et al. 1978a). Theories of the genesis of pathological (congenital) nystagmus will be discussed in Chapter 2.

1.7 Stabilising Eye Movements

Stabilising eye movements are those that are present in order to stabilise the retinal image during self locomotion. These types of movements are important as, without them, the retinal image would "slip" during self locomotion having a deleterious effect on visual acuity (Burr and Ross 1982; Leigh and Zee 1999). There are two different types of stabilising movement: Vestibular Ocular Reflex (VOR) and Optokinetic Nystagmus (OKN).

1.7.1 Vestibular Ocular Reflex (VOR)

Dodge (1903) defines VOR as "those movements of the eyes by which the constant fixation of an unmoved object of interest is maintained during rotation of the head." The movements of the head are detected by three semi-circular canals in each inner ear, and each canal is linked to a pair of extra ocular muscles (Leigh and Zee 1999). The movements produced are seen to be in the opposite direction but of equal magnitude to the movement of the head which elicits them (Dickman 1996). The VOR does not need good (or indeed any) vision in order to occur (Robinson et al. 1984). The eye movements linked to VOR are controlled entirely by the vestibular nuclei, namely the medial vestibular nucleus (MVN), the lateral vestibular nucleus (LVN) and the dorsal vestibular nucleus (DVN) (Dickman 1996;

Leigh and Zee 1999). For simplicity, we will look at a horizontal rotation of the head to the right. The horizontal canals of each ear send signals to the MVN of their corresponding vestibular nuclear complex. Signals are passed from the excited right MVN to the contralateral abducens nucleus which, in turn, via the abducens (VI cranial) nerve, initiates contraction of the ipsilateral lateral rectus muscle. The abducens nucleus, as with saccades, sends signals via the abducens interneurons along MLF to the contralateral oculomotor nucleus, which in turn innervates the ipsilateral medial rectus (Leigh and Zee 1999). This creates a movement of both eyes to the left when the head is turned to the right in the horizontal plane (Dickman 1996; Leigh and Zee 1999). This excitatory pathway is shown diagrammatically in figure 1.8. Inhibitory mechanisms, i.e. driven by the inhibited left MVN as well as ipsilateral projections from the right MVN, also operate to comply with Sherrington's law.

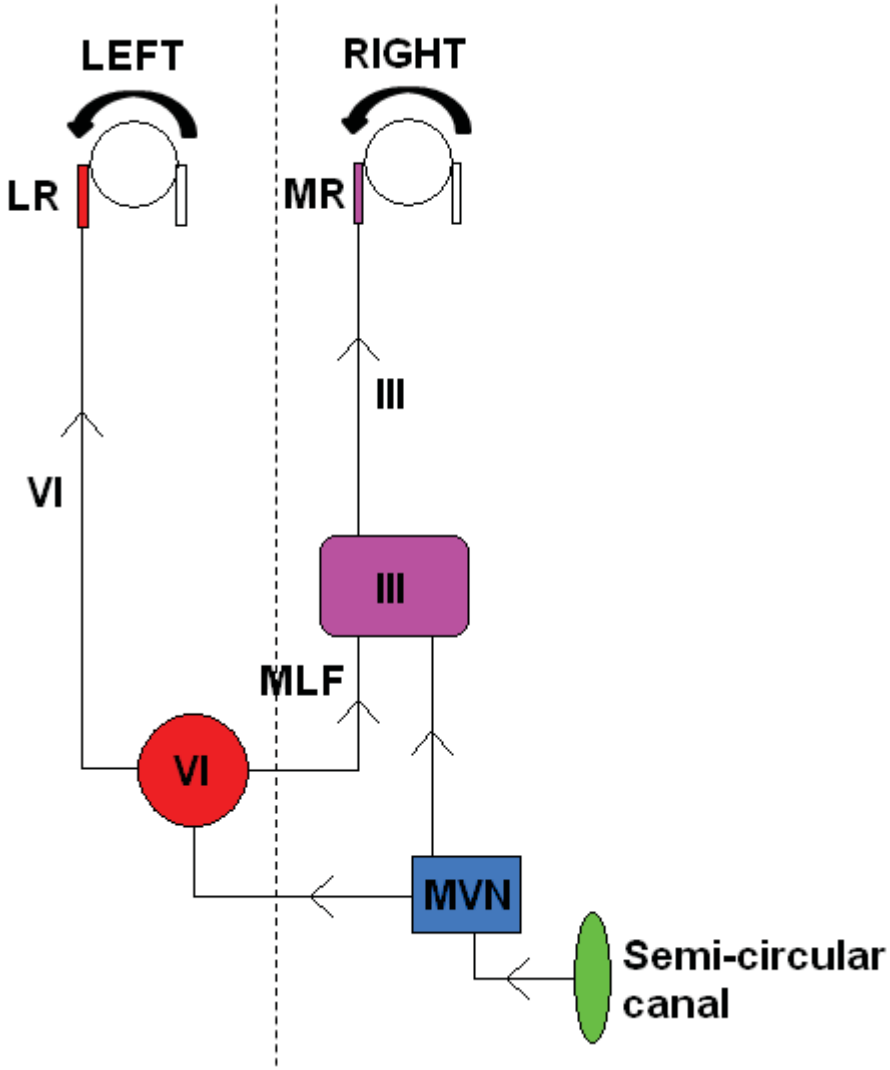

Figure 1.8: Diagrammatic view of the excitatory neural pathway for VOR in response to a head turn to the right. VI - Abducens nucleus and nerve, III - Oculomotor nucleus and nerve, MLF - Medial longitudinal fasciculus, LR - Lateral rectus, MR - Medial rectus

1.7.2 Optokinetic Nystagmus (OKN)

Optokinetic nystagmus (OKN) is present during extended rotation of the head, i.e. any retinal slip produced by movement outside the range of VOR, for example spinning a person on a chair. It is also observed when a subject views a visual scene from the window of a moving train. As the scene rushes past, the eyes follow it, but when they reach the extreme eccentric positions in the orbit, there is a fast jerk of the eyes back to a central location. This indicates that OKN is produced in response to the movement of the image of the world

across the retina, otherwise termed “retinal slip”. The smooth movement of the eyes is generated from the smooth pursuit system. The movement is equal in speed to the movement of the visual scene (up to its maximum limit) in order to keep the image stable on the retina (Leigh and Zee 1999; Longstaff 2005b). The slow phase of OKN, although generated from several of the same brain centres involved in the smooth pursuit system, is in response to movement of the whole visual field rather than a small target (Leigh and Zee 1999). When the eyes reach the extremes of gaze, a saccadic like movement is used to move it back to the primary position (May and Corbett 1996).

1.8 Summary

This chapter has briefly introduced the visual system, the extraocular muscles and the need for the various types of eye movement to keep the image of interest stable on the retina. As nystagmus is an eye movement disorder that produces inappropriate image motion, it was important to establish the normal mechanisms that underlie good vision. The following chapter provides some background to nystagmus, which is the focus of the experiments described in this thesis.

Chapter 2: Nystagmus

2.1 Introduction to Nystagmus

2.1.1 Definition of Nystagmus

Nystagmus is a constant, involuntary movement of the eyes which is typically horizontal (however, vertical and torsional forms of nystagmus can also be seen) and, in the case of infantile nystagmus, presents within the first six months of life (Dell'Osso and Daroff 1975; Casteels et al. 1992; Leigh and Zee 1999; Abadi 2002; Abel 2006). With the exception of infantile nystagmus syndrome (INS) and fusional maldevelopment nystagmus syndrome (FMNS), pathological nystagmus may be termed “acquired” (section 2.1.3). The movements of the eyes are both bilateral and conjugate (Dell'Osso 1985; Leigh and Zee 1999; Abadi 2002). The classification of nystagmus has, in the past, been confusing. In 2001, in response to the varied and misleading classification of various eye movement disorders (including nystagmus), the National Eye Institute (NEI) organized the Classification of Eye Movement Abnormalities and Strabismus Workshop (CEMAS) to develop more appropriate nomenclature, creating two groups of nystagmus: physiological and pathological (Avallone et al. 2001). These types will be discussed next.

2.1.2 Physiological Nystagmus

Chapter 1 (sections 1.6, 1.7.1, 1.7.2) has briefly described end-point nystagmus as well as vestibular and OKN responses. As end point nystagmus was only briefly mentioned, a fuller discussion will be given here.

End-point nystagmus is seen in the extremes of horizontal gaze (>30°) as a jerk type waveform (Abel et al. 1978a; Abadi and Scallan 2001). Amplitudes of movements range between 0.2 and 2.5° (Abadi and Scallan 2001) and frequencies in the region of 1-3Hz (Abel et al. 1978b). This type of nystagmus is seen on fixation of an object in eccentric gaze. The eyes drift from fixation back towards the primary position but are moved back to fixation by a saccadic movement (Abel et al. 1978a; Abel et al. 1978b). It is thought that the cause of this drift is a "leaky" neural integrator (as discussed in section 1.6) (Abel et al. 1978a; Leigh and Zee 1999). End-point nystagmus can be split into four types (Figure 2.1) (Abadi and Scallan 2001).

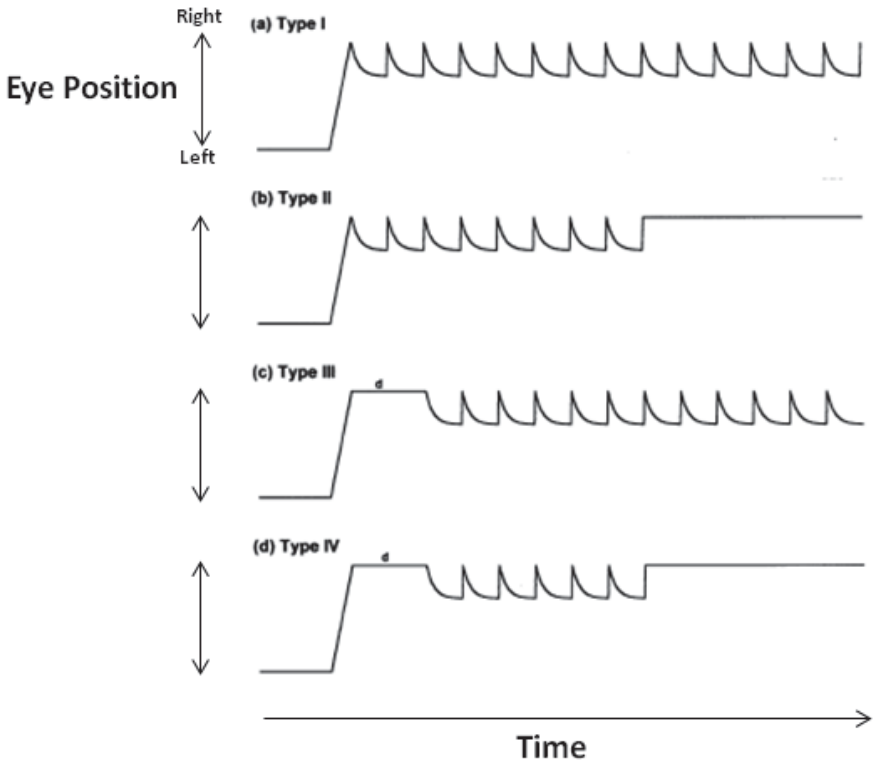

Figure 2.1: Type of end point nystagmus. Type I: no latency of onset and sustained movement. Type II: no latency of onset and un-sustained movement. Type III: latency of onset and sustained movement. Type IV: latency of onset and un-sustained movement (Abadi and Scallan 2001)

Slow phase characteristics typical of congenital nystagmus (decreasing velocity, increasing velocity, linear and pendular) have also been seen in end-point nystagmus (Abadi and

Scallan 2001). It is important to remember that end-point nystagmus is a separate type of nystagmus from gaze-evoked nystagmus, which has pathological causes. End-point nystagmus is found in about 50% of the population and differs from pathological gaze-evoked nystagmus in that it has low amplitude and frequency, is un-sustained and is horizontal without a vertical component on lateral gaze; moreover, patients show no other abnormality on ocular motor examination (Leigh and Zee 1999).

2.1.3 Pathological Nystagmus

The CEMAS classification describes 9 types of pathological nystagmus: Spasmus nutans syndrome, vestibular nystagmus, gaze-holding deficiency nystagmus, vision loss nystagmus, other pendular nystagmus associated with diseases of central myelin, ocular bobbing, lid nystagmus, fusional maldevelopment nystagmus syndrome (FMNS) and infantile nystagmus syndrome (INS) (Avallone et al. 2001). The investigations discussed in this thesis are concerned with INS and so this will be considered in detail in section 2.2. The following sections will briefly discuss the other forms of pathological nystagmus.

2.1.3.1 Spasmus Nutans Syndrome and Vestibular Nystagmus

Spasmus Nutans is a condition with onset in the first year of life that comprises low amplitude, high frequency intermittent nystagmus. This is associated with head nodding and abnormal head posture (AHP) (Leigh and Zee 1999).

In patients for whom the nystagmus is the result of disease of the peripheral vestibular system (i.e. semi-circular canals), a horizontal jerk nystagmus is seen and is generally associated with vertigo (Gottlob 2000; Stahl et al. 2000). If the vestibular system is affected more centrally, i.e. with lesions of the areas of the brain associated with vestibular control,

then a vertical nystagmus is seen (Stahl et al. 2000). Periodic alternating nystagmus (PAN), which will be discussed in section 2.2.1, has also been found as a result of lesions of the central vestibular system (Stahl et al. 2000; Tilikete and Pelisson 2008).

2.1.3.2 Gaze-Holding Deficiency and Vision Loss Nystagmus

As described in section 1.6, neural integration creates the positional commands of the step of innervation from the velocity commands of the pulse of innervation (Leigh and Zee 1999; Stahl et al. 2000; Goldman et al. 2002; Crawford et al. 2003). Gaze-evoked nystagmus is an acquired form of end-point nystagmus, which can result from lesions of the brain centres responsible for neural integration, namely the nucleus prepositus hypoglossi and medial vestibular nucleus in the case of horizontal nystagmus (Leigh and Zee 1999; Stahl et al. 2000; Goldman et al. 2002) and the interstitial nucleus of Cajal in the case of vertical nystagmus (Leigh and Zee 1999; Stahl et al. 2000; Buttner et al. 2002). Lesions of the flocculus of the cerebellum can also cause gaze-evoked nystagmus (Stahl et al. 2000).

Problems with the visual pathway/system can cause nystagmus in two ways: by creating a block to visual perception of a target, or by disrupting the visual signals that fine tune and maintain fixation (Stahl et al. 2000). These problems can manifest in many different ways, from brain tumours to haemorrhages (Stahl et al. 2000; Madill and Riordan-Eva 2004; Tilikete and Pelisson 2008). The disruption of visual fixation results in the eyes drifting away from the object of regard, which is usually corrected for. However, the corrective drifts cause the eyes to move back and forth, and Stahl et al. (2000) showed that this can be demonstrated in subjects without any pathology when attempting to hold fixation in the dark to a remembered location.

2.1.3.3 Other Pendular Nystagmus (associated with diseases of central myelin), Ocular Bobbing and Lid Nystagmus

These classifications refer to nystagmus associated with demyelinating diseases, such as multiple sclerosis, which result in a pendular nystagmus movement (Leigh and Zee 1999; Avallone et al. 2001). Ocular bobbing is a vertical movement of the eyes which usually presents as a fast downward movement of the eyes with a slow recovery (although the reverse can also be seen) (Avallone et al. 2001). Lid nystagmus describes the associated movements of the eyelids in vertical nystagmus (Avallone et al. 2001).

2.1.3.4 Fusional Maldevelopment Nystagmus Syndrome (FMNS)

Fusional maldevelopment nystagmus syndrome encompasses the forms of nystagmus associated with tropias/strabismus and other abnormalities of binocular vision (Gottlob 2000). These forms of nystagmus are Latent and Manifest Latent. Latent nystagmus (LN) is seen when one eye is occluded, and has a jerk movement towards the un-occluded eye (Gresty et al. 1992; Erchul et al. 1998; Abadi and Scallan 2000; Abel 2006). Manifest latent nystagmus (MLN) is a latent form that is present when both eyes are open/un-occluded in the presence of manifest strabismus (Dell'Osso et al. 1987; Dickinson and Abadi 1990; Abadi and Scallan 1999; Abadi and Scallan 2000). It has been suggested that the inability to fuse the retinal images of the two eyes can also cause this form of nystagmus, i.e. in the presence of cataracts, retinal dystrophies, etc. (Dell'Osso et al. 1987; Abadi 2002; Abadi and Bjerre 2002).

Latent and manifest latent nystagmus have a characteristic waveform, with a slow phase of linear or exponentially decreasing velocity (Dell'Osso et al. 1987; Gresty et al. 1992;

Gradstein et al. 1998; Leigh and Zee 1999). Abadi and Scallan (2000) indicate from their findings that MLN can be split into four types depending on the characteristics of the waveform. All types have a classic MLN waveform during monocular viewing, the differentiation being based on the characteristics during binocular viewing. During binocular viewing, type I shows stable fixation (this being termed LN), whereas type II has the presence of square wave jerks, type III has torsional nystagmus, and type IV a horizontal MLN waveform (Figure 2.2) (Abadi and Scallan 2000).

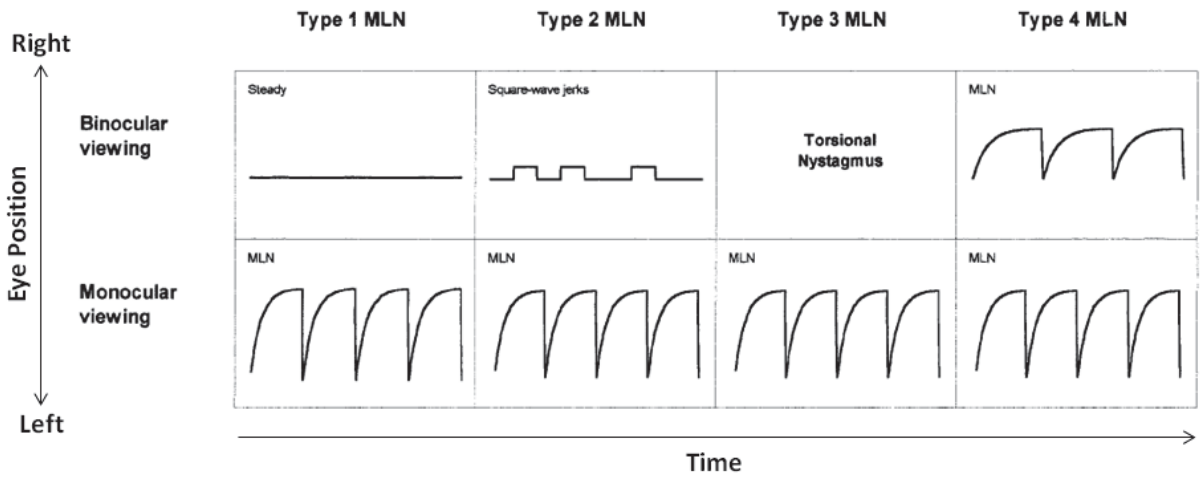

Figure 2.2: The four types of MLN waveform (Abadi and Scallan 2000)

Abadi and Scallan (2000) also describe the presence of six different types of slow phase. They report, in addition to the classic decreasing and linear velocity slow phases, the presence of a saccadic element and also a pendular movement. Some studies have found waveforms characteristic of INS in MLN/LN (Scallan and Abadi 1997; Abadi and Scallan 1999). These will be discussed in more detail in section 2.4. For those subjects with LN, binocular VA is generally normal in the absence of any sensory deficiencies or manifest strabismus. In the presence of manifest strabismus, amblyopia is present in MLN (Gradstein et al. 1998).

2.2 Infantile Nystagmus Syndrome (INS)

Infantile nystagmus syndrome (INS) generally presents within the first six months of life (Anderson 1953; Gottlob 1997; Maldonado and Hertle 2001; Khanna and Dell'Osso 2006). The average age of onset of INS is quoted by Gottlob (1997) as being 1.9 months of age, although there have been reports of rare cases in which nystagmus remains undetected until adult life. Such cases are assumed to be a result of low frequency nystagmus with only a small effect on vision and for a lack of eye care facilities in the area where the patient lived (Abel 2006). Reinecke (1997) describes the development of INS as being split into three phases. The first phase is usually evident at about 2 months of age and involves what is known as triangular waveforms, so called because they have high amplitude and low frequency which in turn produce pyramid like patterns on eye movement recording (section 2.4). During this phase, the patient appears to exhibit no horizontal pursuit movements, but vertical pursuit movements are unaffected. The second phase of development occurs at roughly six months as a low amplitude pendular nystagmus (section 2.4) with a frequency of about 6Hz (amplitude and frequency are described in section 2.5). The third phase occurs at the age of about 18 months, with the onset of a classic jerk nystagmus (section 2.4) with a slow phase and a corrective saccade. The null position (an orbital eye position at which the eye movements are minimal, see section 2.6.2) also develops during phase three.

Some studies have used the classification “sensory nystagmus” or “motor nystagmus” (Cogan 1967; Casteels et al. 1992; Buncic 2004), sensory being nystagmus associated with sensory deficits such as congenital cataracts, albinism/ocular albinism, optic nerve hypoplasia, aniridia, and retinal dystrophies (Abadi 2002; Maybodi 2003; Khanna and Dell'Osso 2006). Motor nystagmus is the term given to nystagmus in the absence of any

apparent sensory abnormality (Buncic 2004). In this situation, it is termed idiopathic INS (Reinecke 1997; Abadi 2002; Maybodi 2003).

2.2.1 Periodic Alternating Nystagmus (PAN) in INS

Periodic alternating nystagmus (PAN) is defined as regular periods of active and quiet phases in a nystagmus waveform (Figure 2.3) (Shallo-Hoffmann et al. 1999).

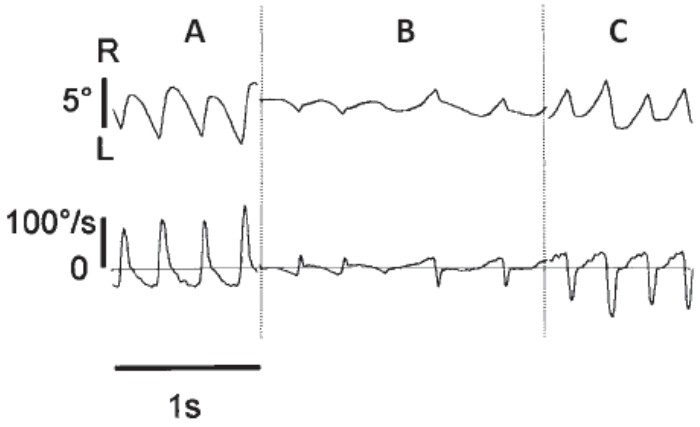

Figure 2.3: Eye movement recordings of a subject with PAN. Top: Eye position, Bottom: Velocity recording. A: First active period (right beating), B: Quiet period, C: Second active period (left beating) (Shallo-Hoffmann et al. 1999)

It was originally thought that this was a relatively rare occurrence, being found in around 9% of subjects (Gradstein et al. 1997). However, this study used only a short duration recording (2-3 minutes). Recordings of 8 minutes have shown the prevalence of PAN to be 38% in subjects with idiopathic INS (Shallo-Hoffmann et al. 1999) and 37.5% in subjects with nystagmus associated with albinism (Abadi and Pascal 1994). A typical PAN cycle consists of a left beating nystagmus followed by a quiet phase and then a right beating nystagmus followed by another quiet phase. This same study reported a median PAN cycle to have a duration of 223s (maximum 307s) (Shallo-Hoffmann et al. 1999).

2.2.2 Prevalence of INS

The reported prevalence of nystagmus varies widely between publications. The main reason for this is because of the different ways in which nystagmus has been classified in the past. The prevalence has been reported to be between 1 in 350 and 1 in 6000 (Hemmes 1924; Anderson 1953; Forssman 1971; Forssman and Ringner 1971; Hu 1987). In studies looking into causes of visual impairment, INS has been reported to be present in between 4.2 and 16% of the visually impaired population (Rogers 1996; Lu et al. 2009) (the RNIB reports the prevalence of visual impairment in the UK to be 2.9% (2011)).

The most recent study into the prevalence of nystagmus is the Leicestershire Nystagmus Survey (Sarvananthan et al. 2009). This survey classifies nystagmus according to the CEMAS nomenclature of INS but also identifies the sub-divisions within this classification. They identify that the total prevalence of INS in the population to be 12 in 10,000 for those under the age of 18, and 14.7 in 10,000 for those over the age of 18. The prevalence of idiopathic INS in those under the age of 18 is placed at 2.9 in 10,000 and 3.2 in 10,000 in INS associated with albinism. FMNS (section 2.1.3.4) has a prevalence of 1 in 10,000, and other visual associations with nystagmus are found in 4.8 in 10,000. For those under the age of 18, the most common ocular association with nystagmus is albinism. For those over the age of 18, the prevalence of idiopathic INS is found to be 3 in 10,000. Nystagmus associated with albinism has a prevalence of 2.2 in 10,000, with FMNS being 0.4 in 10,000. Nystagmus associated with other ocular abnormalities has a prevalence of 8.5 in 10,000. The most common relationship for the over 18 age group was shown to be nystagmus associated with retinal disease and other causes of low vision (Sarvananthan et al. 2009).

The main focus of this thesis is on visual function in INS, and therefore the rest of this chapter will concentrate on this type of nystagmus.

2.3 Theories of the Causes of Nystagmus

There are many different models proposed for the causes of INS. These models include defects of the vestibular system, saccadic system, optokinetic system, fixational system, and the neural integrator (Casteels et al. 1992). Many of the models suggest a neural miswiring. However, the fact that nystagmus is associated with many ocular abnormalities that affect vision indicates an underlying visual cause, even if it has not yet been identified (Casteels et al. 1992).

The first model of INS was suggested by Dell'Osso in 1967 (Abadi 2002), who hypothesised a defect in the slow pursuit eye movement system. Since then, many other models have been proposed. Optican and Zee (1984) modelled a system based on abnormal neural integration. The neural integrator receives both position and velocity feedback loops. Normally, the position feedback would be positive and the velocity negative (cancelling each other to give steady fixation). They proposed that, in the case of INS, the velocity feedback is positive, not negative, hence resulting in unstable integration (Optican and Zee 1984). A number of different types of INS waveform were produced by their computer model.

Broomhead et al. (2000) proposed that nystagmus is borne of an abnormality of the saccadic system, giving rise to a problem in saccadic termination. Saccades are programmed by the relationship of the dynamic motor error, i.e. the difference between the gaze angle at which the eye needs to be and the current eye position. This model suggests an abnormal relationship between the burst of innervation from the EBNs and the motor error that

programmes the size of the saccade (Broomhead et al. 2000). This theory contradicts the neural integrator theory set out by Optican and Zee (1984), which only demonstrates nystagmus waveforms in eccentric gaze. Broomhead et al. (2000) report that abnormalities of the burst neurons explain the presence of micro saccadic oscillations and how voluntary saccades interact with INS. As with the model of Optican and Zee (1984), Broomhead et al.'s model displays some but not all types of INS waveform.

Jacobs and Dell'Osso (2004) developed a model that suggests a lack of dampening in the smooth pursuit system. At the start of a pursuit movement, a dampening of the oscillation (termed "ringing" by Jacobs and Dell'Osso) occurs, which then shows an exponential decay. In this model, the dampening is switched off, and the oscillation allowed to continue. This then demonstrates a pendular type waveform (Jacobs and Dell'Osso 2004). Jacobs and Dell'Osso demonstrated that their model can also perform all the "normal" oculomotor system tasks that are required, such as smooth pursuit and voluntary saccades, etc. This model, however, still only reproduces the pendular waveform variations (P, PP, P_{FS}, PP_{FS}) without the jerk waveforms.

It was suggested by Harris and Berry (2006) that nystagmus is, in fact, a compensatory mechanism. They suggest that, when poor sensitivity to high spatial frequencies is present at an early age, the contrast can be improved by a certain degree of movement of the visual image, as well as by placing the image on the fovea. As these two mechanisms are in fact contradictory to one another, a compromise must be met, i.e. the eyes must position the object of regard on the fovea, but must also move. The model created by Harris and Berry displays smooth oscillations with increasing velocity. In the case of jerk nystagmus, the saccadic system is employed to return the eyes to fixation (Harris and Berry 2006). This

model is capable of demonstrating a number of nystagmus waveforms associated with INS, including the jerk and pendular waveforms. Indeed, Harris and Berry indicate that, when a neural integrator type mechanism is introduced, a null position is even produced. From this model, it was concluded that INS is a compensatory mechanism adopted by infants soon after birth. If an infant's vision is compromised in some way (e.g. albinism) the movement of the retinal image acts to improve visual function. According to their hypothesis, any number of visual impairments or even some delay of foveal development can cause the eyes to move in order to enhance visual function. If this continues once the plastic (critical) period finishes, then INS persists throughout life. Harris and Berry argue that this model accounts for the development of nystagmus early in life, and so indicates that any treatment or intervention must be performed at this time, i.e. whilst still in the plastic period (Harris and Berry 2006).

INS also displays genetic links, being inherited in a dominant, recessive and x-linked manner (Kerrison 1999; Self and Lotery 2007); the most common form is x-linked (Cabot et al. 1999; Self and Lotery 2007). In 1999, both Cabot et al. (1999) and Kerrison et al. (1999) found close linkages to chromosomes Xp11.4-p11.3 and Xq26-q27, respectively. More recently, chromosome Xq24-q26.3 was linked to INS in one family by Self et al. (2006). Mutations of the OA1 gene, generally associated with x-linked ocular albinism, have also been found in patients with nystagmus with no signs of albinism (Preising et al. 2001). In recent years, X-linked INS has been associated with mutations of the FRMD7 gene, this first being discovered by Tarpey et al. (2006). From 2006 to 2007, 28 mutations associated with nystagmus were found in FRMD7 (Self and Lotery 2007). The number of identified mutations currently stands at 41 (Li et al. 2011). The exact way in which FMRD7 or indeed any gene

mutations relate to nystagmus is not fully understood. However, recent research has show that FRMD7 is mainly expressed in the brainstem of foetal brains. FRMD7 could therefore have a significant influence in the development of the oculomotor centres of the brain (Pu et al. 2011).

The wide variety of models that produce INS waveforms, as well as the variety of genetic links found, is supportive of the theory that nystagmus is in fact a manifest symptom of a number of different conditions (Kerrison 1999; Evans 2007). As a result, the underlying cause of nystagmus must be determined in order to properly evaluate, treat and advise a particular patient.

2.4 Nystagmus Waveforms

When investigating nystagmus, the type of waveform can indicate the causative factor of the nystagmus and therefore aid in its diagnosis (Leigh and Zee 1999). Dell'Osso and Daroff (1975) reported findings from their research and proposed that there are twelve separate types of nystagmus waveform, which can be grouped under three categories: pendular, jerk and dual (Table 2.1).

In the discussion of nystagmus waveforms, the terms slow phase and fast phase are commonly used. The slow phase is the smooth movement of the eyes away from fixation. The fast phase is the corrective saccade often used to re-foveate the eyes (Figure 2.4) (McIntyre 1939; Erchul et al. 1998; Abel 2006).

Group		Waveform Type	Description
Pendular (Figure 2.5)		Pure Pendular (P)	Slow movements of the eyes from side to side
		Asymmetric Pendular (AP)	Similar to P but skewed in a particular direction
		Pendular with foveating saccades (P_{FS})	P form with saccades at either the peaks or troughs
Jerk (Figure 2.7)	Unidirectional	Pure Jerk (J)	Slow phase of constant velocity with a fast corrective saccade
		Jerk with extended foveation (J_{EF})	Increasing velocity slow phase with periods of foveation
		Pseudo-Cycloid (PC)	Slow phases re-foveate the eyes as the saccade is not sufficient
		Pseudo-Jerk (PJ)	Slow phases re-foveate the eyes as the saccade is not sufficient
	Bidirectional	Pseudo-Pendular (PP)	Small saccades at both extremes of movement
		Pseudo-Pendular with foveating saccades (PP_{FS})	As PP but one of the saccades is larger and re-foveates the eyes
		Triangular (T)	As PP but the slow phases are of constant velocity
		Bidirectional Jerk (BDJ)	As T but one saccade is larger and re-foveates the eyes; fixation is then maintained for a short time
Dual (Figure 2.8)		Dual Jerk (DJ)	Combination of J and P forms. J is the predominant form with P superimposed on the slow phases

Table 2.1: Information regarding the 12 types of nystagmus waveform (Dell'Osso and Daroff 1975)

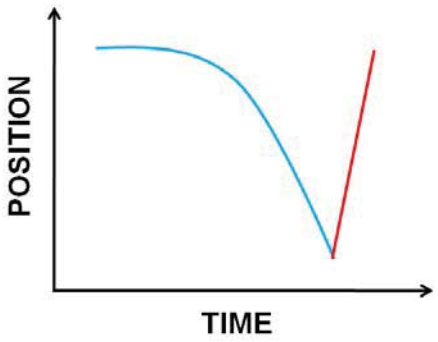

Figure 2.4: Waveform showing the slow phase (blue) and fast phase (red) of a nystagmus waveform

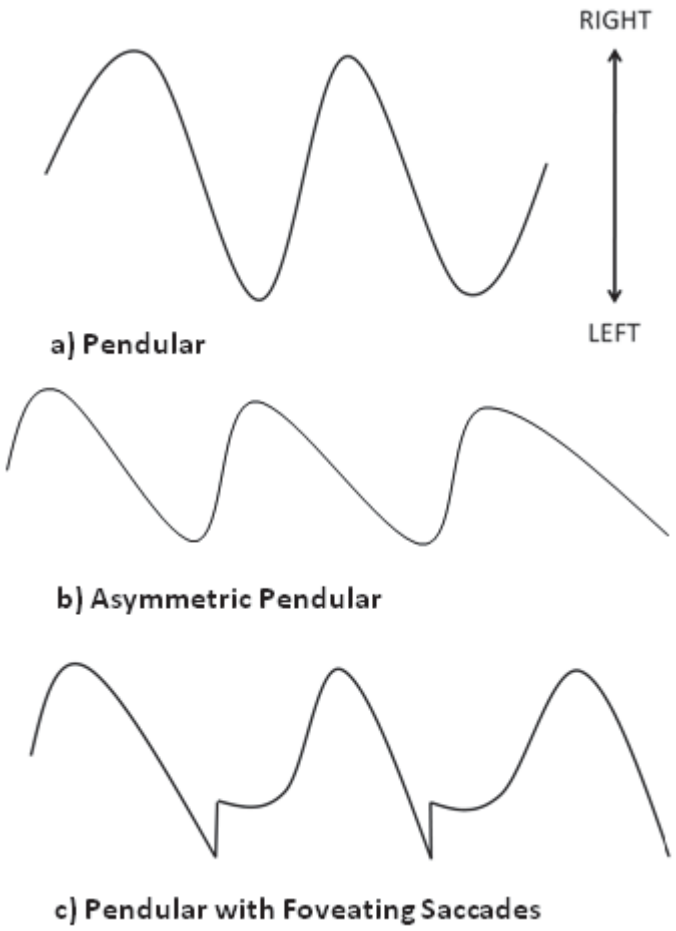

Figure 2.5: Pendular nystagmus waveforms. a) Pendular, b) Asymmetric Pendular, c) Pendular with Foveating Saccades (Adapted from Abadi 2002)

Pendular nystagmus waveforms consist of mainly slow phases (Figure 2.5). Jerk nystagmus comprises slow and fast phases. The slow phase may present as an eye movement with either constant velocity, decreasing velocity or increasing velocity (Figure 2.6).

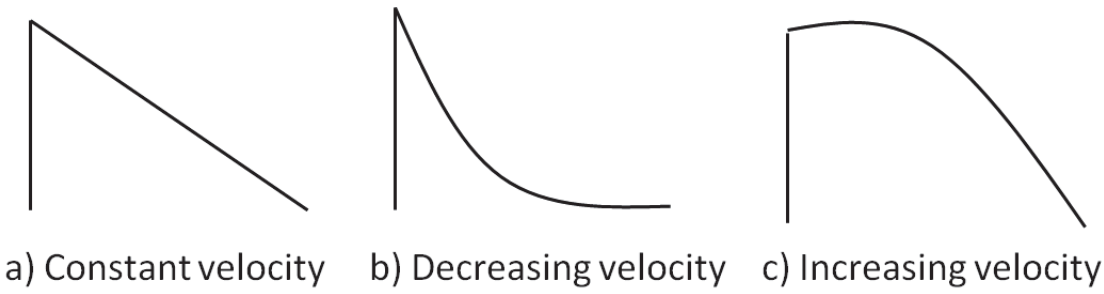

Figure 2.6: Different velocity patterns of the slow phase in nystagmus (Adapted from Leigh and Zee 1999)

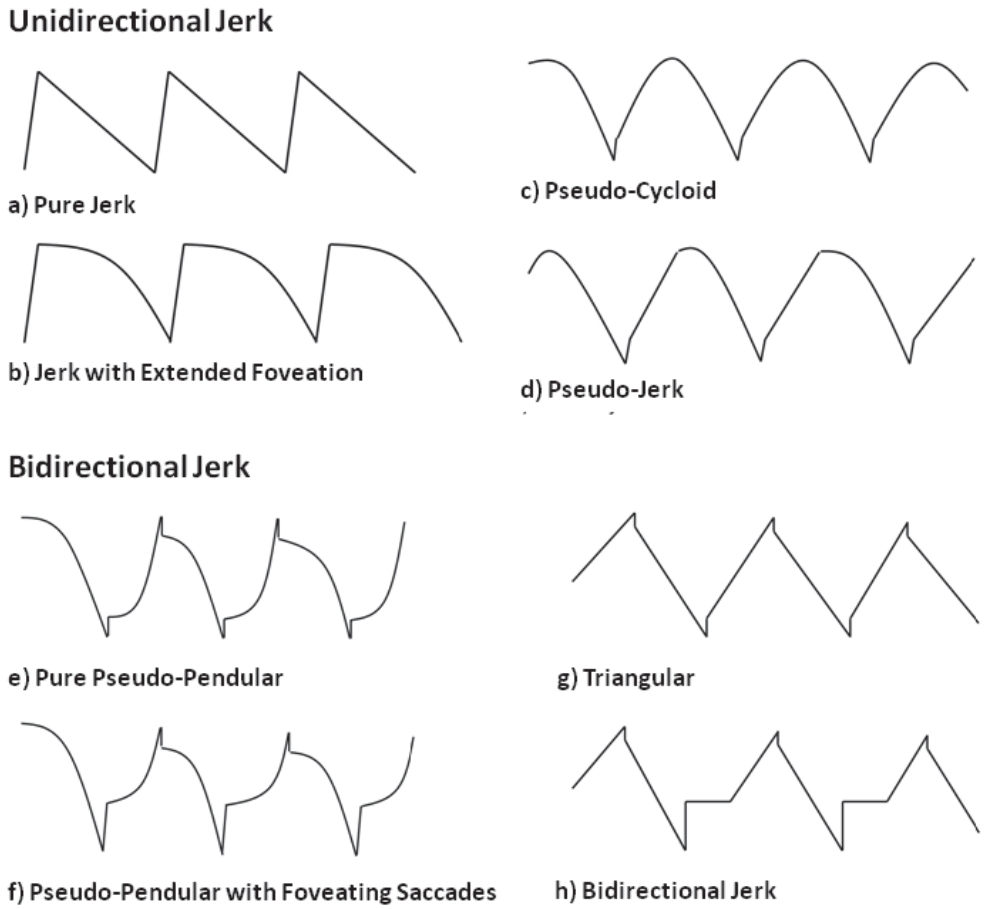

Figure 2.7: Jerk nystagmus waveforms (Adapted from Dell'Osso and Daroff 1975)

Figure 2.8: Dual jerk waveform with pendular waveform on the slow phases (Adapted from Dell'Osso and Daroff 1975)

Interestingly, it has been noted that a single subject with INS can exhibit several different waveforms (Dell'Osso et al. 1972; Clement et al. 2002). This has also been indicated in

development by Reinecke (1997), who describes, in the same child, triangular, pendular and jerk waveforms in the first 2 years of life.

2.5 Waveform Parameters

In nystagmus research, the waveforms are analysed on the basis of their amplitude, frequency and intensity as well as their appearance, as mentioned in section 2.4. In this section, we will define these parameters and discuss their characteristics in relation to nystagmus.

2.5.1 Amplitude

The amplitude is a measure of how far from fixation the eyes move. On a waveform, this is seen as the height of the wave (Figure 2.9). The amplitude of the waveform is linked to the velocity of the foveating saccade by the "main sequence" (see chapter 1) (Bahill et al. 1975b). Abadi and Bjerre (2002) reported amplitudes with a range of between 0.3-15.7° in a study of 224 people with nystagmus.

The amplitude of nystagmus is affected by fixation attempt, visual demand, and stress (Dell'Osso 1973; Wiggins et al. 2007; Cham et al. 2008a). Subjects with nystagmus typically show an increase in the amplitude of the waveform when asked to fixate an object compared to, for example, looking into the distance (Dell'Osso 1973). As well as fixation attempt, "effort to see" was also thought to cause a worsening of nystagmus waveform (Abadi and Dickinson 1986). However, Wiggins et al. (2007) showed that an increase in visual demand (in the absence of stress) actually reduces nystagmus amplitude. In contrast, stress has been shown in recent studies to cause an increase in nystagmus amplitude (Cham et al. 2008a). These studies will be discussed in more detail in section 2.9.3.

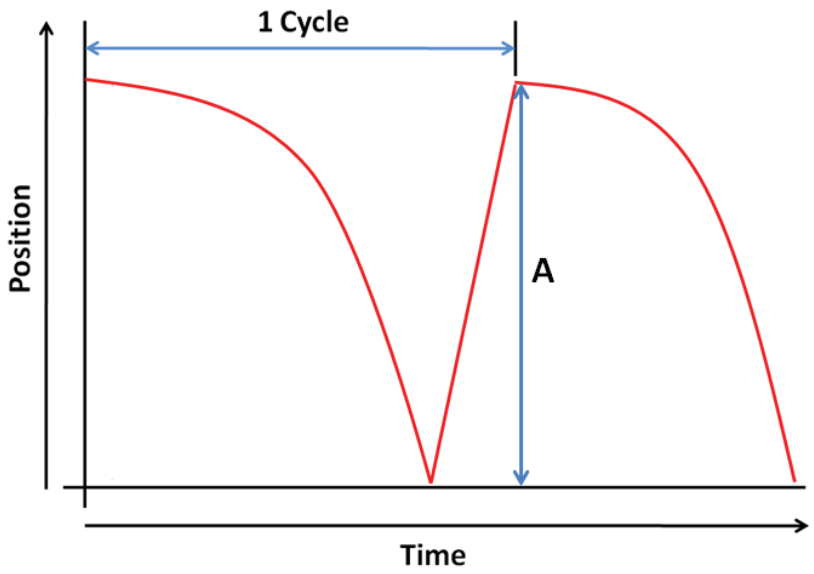

Figure 2.9: Amplitude and frequency of waveforms. A - amplitude

2.5.2 Frequency

The frequency of nystagmus is taken as the number of cycles per second (Hz), a cycle comprising a slow phase and a fast phase. As with amplitude, frequency can vary within and between subjects (i.e. 0.5 - 8Hz) (Abadi and Bjerre 2002). Although Dell'Osso reported changes in the amplitude of nystagmus waveform with fixation, no report was given as to the effects of fixation on frequency (Dell'Osso 1973). Wiggins et al. (2007) demonstrated a reduction in frequency with increased visual demand. Conversely, Cham et al. (2008a) showed an increase in nystagmus frequency under stressful conditions.

2.5.3 Intensity

The intensity of the nystagmus waveform is defined as the product of amplitude and frequency. This gives us a value that is easily comparable across subjects and within the same subject during different situations. As a result of the way in which intensity is calculated, it can easily be seen that an increase in either amplitude or frequency, or even both, will result in an increase in intensity. The converse is true for a decrease in one or both

waveform parameters. Many studies use comparisons of intensity as the preferred measure of changes in waveform parameters (Abadi et al. 1980; Ukwade and Bedell 1992; McLean et al. 2007; Wiggins et al. 2007; Cham et al. 2008a)

We have already mentioned that the parameters of the nystagmus waveform (amplitude, frequency and intensity) are highly variable between subjects, as well as within subjects, depending on fixation attempt, visual demand and stress. These parameters can also be affected by gaze angle (i.e. eye position in the orbit) (Dell'Osso 1973; Abadi and Sandikcioglu 1974).

2.6 Maximising Visual Potential

In this section, we will discuss the aspects of nystagmus that aid or improve vision/VA. In particular, we will discuss the foveation period, the use of null positions and head nodding.

2.6.1 Foveation Period

The foveation period is the term used to describe the period of time in which the position of the image of the object of regard on the retina and the retinal slip velocity allow best visual acuity (Dell'Osso and Daroff 1975; Dell'Osso et al. 1992; Erchul et al. 1998; Leigh and Zee 1999). The movements of the eyes seen in nystagmus can generate retinal slip velocities of up to 180°/s (Abadi and Worfolk 1989). As discussed in section 1.4.1, image motion must be kept below a particular angular velocity to maintain optimal VA. Because of this, it would be expected that those with nystagmus have reduced VA as a result of retinal slip. However, there are subjects with nystagmus who demonstrate average or even above average VA in the absence of any underlying sensory abnormalities (Abadi and Dickinson 1986; Bedell and

Loshin 1991). This surprisingly good VA has been attributed to the presence of foveation periods in the nystagmus waveform (Dell'Osso et al. 1992).

If we first consider the velocity criteria for foveation, we can start with the work of Westheimer and McKee (1975). As discussed in section 1.4.1, Westheimer and McKee placed this value at 2.5°/s, i.e. the fastest retinal image motion for optotypes that did not degrade VA. Burr and Ross (1982) found that, for lower spatial frequencies, somewhat higher image velocities actually aid VA. Leigh and Zee (1999) indicate a threshold of retinal image motion of 5°/s. These values are for "normal" subjects, and so now we must consider how these values affect the criteria used to define foveation in those with nystagmus. The range of velocities used in publications for foveation ranges from 1.67 to 10°/s (Dickinson and Abadi 1985; Bedell and Loshin 1991; Dell'Osso et al. 1992). Because of this range, comparisons are hard to make, and so Chung and Bedell (1996) conducted an investigation to identify the retinal image velocity at which VA is worsened. This was done by moving a Landolt C stimulus across the retina of "normal" subjects in a way that simulated a nystagmus waveform. Varying lengths of foveation were also simulated (20, 40, 60 and 100ms). At velocities of 4°/s or less, Chung and Bedell (1996) found a systematic improvement in VA as foveation duration increased. At higher simulated velocities (i.e. greater than 8°/s), VA was poorer at a foveation duration of 20ms, but asymptotes at foveations of 40ms or longer. Chung and Bedell also calculated critical velocities (above which VA was worse) and found this to be 6.5°/s for foveation durations of 20ms, and 3.7°/s for durations of 40, 60 and 100ms for a change in acuity of 0.1 log units. For a change of 0.05 log units, these values were found to be 4.2 and 2.5°/s, respectively (Chung and Bedell 1996). It was therefore concluded that the threshold velocity for foveation should be about

2-3°/s. In fact, many publications have used a velocity of ≤ 4°/s to identify foveation (Dell'Osso et al. 1992; Dell'Osso et al. 1997; Cesarelli et al. 2000; Bifulco et al. 2003).

As well as velocity, position of the image with respect to the fovea (i.e. fixation accuracy) must also be considered when identifying foveation periods. Dell'Osso and Jacobs (2002) state that "simultaneous satisfaction" of both velocity and position criterion are needed for foveation. As described in section 1.2, the highest density of cone photoreceptors (and therefore the site of most detailed vision) is found within 0.2° of the centre of the fovea (Curcio et al. 1990). Leigh and Zee (1999) state that, for best VA, the object of regard needs to be within 0.5° of the foveal centre. This latter position criterion has been used in many investigations relating to nystagmus (Dell'Osso et al. 1992; Cesarelli et al. 2000; Bifulco et al. 2003; Pasquariello et al. 2009). However, many people with nystagmus do not display such a high degree of accuracy in their waveform, showing a variation in eye position between foveations of greater than 0.5° (Cesarelli et al. 2000; Dell'Osso and Jacobs 2002; Bifulco et al. 2003; Pasquariello et al. 2009). Consequently, Dell'Osso and Jacobs (2002) increased the parameters for defining foveation in their "Nystagmus Acuity Function" (NAF – a predictor of optimal VA based on eye movement recordings) to generate the "eXpanded Nystagmus Acuity Function" (NAFX) (Section 2.8.1). The parameters required for the detection of foveation were gradually increased from 0.5 to 6° for position, and 4 to 10°/s for velocity. Each combination of these values was then compared to the NAF. Those combinations that yielded a result within 10% of the NAF outcomes were then suggested for use with the NAFX. The resulting expanded criterion was ±3° from the fovea for position, and <4°/s for velocity (Dell'Osso and Jacobs 2002).

Cesarelli et al. (2000) studied the standard deviation of the position (SDp) of the eyes between the average position of the eyes during foveation and found all but one of their subjects to have SDp of greater than 0.5°, indicating that a strict position criteria is not useful. The position criterion was suggested as being within ±0.5° of the positional maximum or minimum of any particular cycle rather than position with respect to the target (Cesarelli et al. 2000). VA appears to be worse in people who demonstrate a larger SDp (Cesarelli et al. 2000). Bifulco et al. (2003) and Pasquariello et al. (2009) describe the presence of a baseline oscillation (BLO) (Figure 2.10) within the nystagmus waveform that accounts for some part of the inaccuracy of foveation. Bifulco et al. (2003) found that BLO amplitude ranges from 0.39 – 4.17° with the average being 1.31°. A positive correlation between the SDp and BLO amplitude was found. If we then consider the findings of Cesarelli et al., the larger the BLO amplitude, the worse VA becomes (Cesarelli et al. 2000; Bifulco et al. 2003).

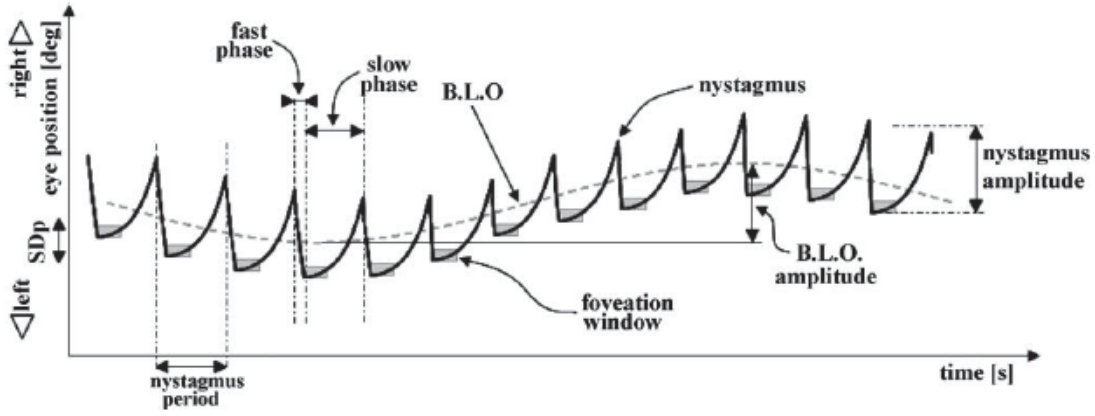

Figure 2.10: Diagram showing the nystagmus waveform and BLO (Pasquariello et al. 2009)

The variation in cycle to cycle position has led to an equally variable position criterion for foveation in the literature. Dell'Osso and Jacobs (2002) suggest that it be extended to ±3°, but other studies have used a position of ±2° (Ukwade and Bedell 1992; Wiggins et al. 2007).

A criterion of ±2° allows for the average amplitude of the BLO (Bifulco et al. 2003) and would therefore encompass a number of foveations that would be otherwise excluded with the more strict criterion of ±0.5°.

Many studies have shown a correlation between the duration of the foveation period and visual acuity (i.e. longer foveation provides better acuity) (Dell'Osso and Daroff 1975; Dickinson and Abadi 1985; Abadi and Worfolk 1989; Chung and Bedell 1996; Cesarelli et al. 2000; Pasquariello et al. 2009). However, no correlation between foveation duration and VA was found by Bedell and Loshin (1991). An explanation for these differences could be the variability in the position and velocity criteria used to identify the foveation periods. The distribution of visual acuities in nystagmus subjects who display extended foveation ranges from -0.1 to 1.0 LogMAR (Abadi and Bjerre 2002). However, no associated foveation period durations were presented to accompany these results. Abadi and Bjerre (2002) also grouped together both those with idiopathic nystagmus and those with associated sensory deficits, and so no differentiation between the effects of the visual impairment and the nystagmus per se can be made.

2.6.2 Null Point

The null point is the position of the eyes within the orbit at which the velocity of the slow phase is at its minimum (Dell'Osso et al. 1972; Leigh and Zee 1999), or where the nystagmus is said to be “damped” (intensity is minimal) (Khanna and Dell'Osso 2006; Weiss and Kelly 2007). In the case of PAN (section 2.2.1), a dynamic null position may be present (i.e. more than one null position) (Abadi and Bjerre 2002). It is argued that, in this position of gaze, the features of the nystagmus waveform (i.e. intensity and foveation duration) allow for best visual acuity (Calhoun and Harley 1973; Yang et al. 2005; Serra et al. 2006). In a study of 143

people with nystagmus, Abadi and Bjerre (2002) reported that, of those subjects who exhibited a null position, 73% were within ±10° of the primary position. The remaining 27% had a null position at or greater than ±20° eccentricity, all of whom demonstrated an abnormal head posture (Abadi and Bjerre 2002). The distribution of null positions in the population examined by Abadi and Bjerre (2002) varied between -40° and +40° (negative values indicate left, and positive indicate right).

Head postures are used to place the eyes at the null point whilst keeping gaze straight ahead relative to body position (Leigh and Zee 1999). Abadi and Bjerre (2002) found that 69% of subjects used an abnormal head posture at some time, even those with a null position within ±10°. Surgery can sometimes be performed in order to correct for an abnormal head posture by shifting the null position. This will be discussed in more detail in section 2.10.2.

If subjects adopt a gaze angle that is away from their preferred null position, then the intensity of the nystagmus waveform is seen to be more extreme (Calhoun and Harley 1973; Dell'Osso 1973; Reinecke 1997; Yang et al. 2005; Khanna and Dell'Osso 2006).

Often subjects with nystagmus also demonstrate reduction (and sometimes cessation) of nystagmus eye movements on convergence (Gamble 1934; Abel 2006). Abadi and Dickinson (1986) report that 8% of 150 subjects examined have a convergence null position. In a population of 117, Abadi and Bjerre (2002) found 44% exhibited such a convergence null, with a greater effect when the viewing distance was closer than 25cm. The differences seen between these two studies are difficult to explain. Both studies originate from the same laboratory, the data of the latter being a compilation of records from patients seen over a number of years. The study by Abadi and Dickinson (1986) assessed eye movement

recordings of patients viewing targets placed at distances along the midline at 50, 33 and 15cm. The study by Abadi and Bjerre (2002) simply reports the findings from previous records and does not state how convergence null was identified. It is possible that the reason for the differences observed relates to different criteria being used for identification.

2.6.3 Head Nodding

Abadi and Bjerre (2002) found that 27% of 143 subjects with nystagmus exhibited head nodding. In the case of nystagmus, head nodding is generally seen when subjects carry out a visually demanding task, but it is not a compensatory process (Khanna and Dell'Osso 2006). Based on the work of Sheth et al. (1995), Khanna and Dell'Osso (2006) attribute head nodding to the neural signals that drive nystagmus also having an effect on the neck muscles. In their investigation, Sheth et al. (1995) used afferent stimulation of the forehead and neck with both vibration and electrical impulses to modify their nystagmus waveform. They found that vibration was the best stimulus, with the optimum location being the neck, having a positive effect on foveation duration (no quantitative data presented) in 80% of their subjects (Sheth et al. 1995). Khanna and Dell'Osso (2006) further suggest that head nodding cannot be a compensatory mechanism as VOR would counteract the effects of the head movement. Carl et al. (1985) indicate that, for head nodding to be compensatory in INS, VOR must be abnormal and the head nodding must be closely correlated to the nystagmus. Out of 5 subjects, only one was found to use head nodding as a compensatory mechanism. It is suggested that the INS waveform interferes with the development and calibration of VOR due to inappropriate retinal slip, resulting in low VOR gain (Carl et al. 1985). It was concluded that, in the other subjects, head nodding was a tremor associated with the nystagmus (Carl et al. 1985).

In the case of Spasmus Nutans (a childhood condition whose features include small amplitude high frequency nystagmus, head nodding and abnormal head posture) (Leigh and Zee 1999), head nodding is thought to be a compensatory mechanism, which uses the vestibular system to move the eyes (Reinecke 1997). The head nodding in this situation causes elimination of the eye movements for brief moments (Carl et al. 1985). Carl et al. (1985) suggest that, in this situation, VOR gain must be normal so as not to create retinal slip as a result of head nodding, which would otherwise reduce VA.

2.7 Oscillopsia

Oscillopsia is the illusionary perception of movement of the world and is a common symptom of nystagmus acquired after infancy (Leigh and Zee 1999). However, in those patients with congenital/infantile nystagmus, oscillopsia is rarely reported, despite the constant movement of the eyes (Leigh et al. 1988; Abel et al. 1991; Bedell 1992; Bedell and Bollenbacher 1996). Leigh et al. (1988) suggest that people with INS use extra-retinal signals to counteract the effect of the image motion. In this model, efference copy of the waveform effectively cancels out the signal of the image motion across the retina, resulting in a stable perception. This theory is also proposed by Bedell et al. (1993; 1996) and Abadi et al. (1999). Other suggested reasons for the lack of oscillopsia include an increased threshold to image motion and the possibility of suppression during nonfoveating periods (Abel et al. 1991).

The idea of suppression was discounted by Goldstein et al. (1992), who presented spot laser flashes throughout the waveform at two locations positioned to the right or left of a fixation target at an angle of half the amplitude of the nystagmus waveform. Subjects responded over a wide range of eye velocities indicating that they were able to detect the stimulus

during eye movement. When asking subjects to locate the stimulus, Goldestein et al. (1992) found that, even when the eyes had moved to a position where, for example, the stimulus on the left of the fixation target now appeared in the right visual field, the stimulus was still localised by the subject as being on the left of fixation (the fixation target was removed during presentation of each stimulus). The suggestion was then made that subjects with nystagmus shift their visual map of the world, in synchrony with their nystagmus, in order to avoid oscillopsia (Goldstein et al. 1992). However, this was only demonstrated for a small number of subjects and does not account for the fact that some people with congenital nystagmus experience oscillopsia on some occasions (Abel et al. 1991); oscillopsia is experienced more frequently in positions of gaze that increase nystagmus amplitude and reduce foveation.

As is the case with many factors relating to nystagmus, there is a great deal of contradictory data in the literature with regards to the suppression of oscillopsia, indicating that this is perhaps an area that needs to be researched in more detail using strict criteria for the classification of the nystagmus with which people present. Although oscillopsia is usually not experienced by those with INS, if the retinal image is stabilised, oscillopsia is experienced (Leigh et al. 1988).

2.8 Visual Function

2.8.1 Visual Acuity (VA)

Visual acuity (VA) shows a large variation in people with nystagmus, ranging from -0.3 to 2.0 LogMAR (Abadi and Pascal 1991; Abadi and Bjerre 2002). When different types of INS are considered separately, idiopathic INS has a better average VA (+0.35 LogMAR) than that

associated with albinism and visual abnormalities (+0.67 and +0.55 LogMAR, respectively) (Abadi and Pascal 1991; Abadi and Bjerre 2002). In the case of albinism, Weiss et al. (2011) compared the clinically measured VA of subjects with nystagmus to the dynamic visual acuity (DVA) data of non-nystagmus subjects recorded by Demer and Amjadi (1993) (log-linear relationship between retinal slip and VA). The VA measured with Snellen letters (subjects over age of 3) or Teller Cards (subjects younger than 3) was worse than predicted by the DVA relationship. It was therefore concluded that the reduction in the VA of those people who have INS associated with albinism is a result of foveal hypoplasia not of the movements of the eyes (Weiss et al. 2011).

The VA of persons with nystagmus is often reported as being poorer than that of “normal” observers (Abadi and Pascal 1991; Chung and Bedell 1995, 1997; Simmers et al. 1999). However, some subjects can obtain near normal acuities of better than 0.0 LogMAR (Abadi and Dickinson 1986; Bedell and Loshin 1991). As discussed in section 2.6.1, this is thought to be due to the presence of foveation periods in the nystagmus waveform. Studies have attempted to measure the reduction in VA as a result of nystagmus eye movements by moving targets across the retina of “normal” observers (Chung and Bedell 1995, 1996, 1997). By using a mirror galvanometer to create nystagmus type retinal image motion in “normal” patients, foveation periods of 40 and 120ms were simulated. VA was worse for both foveation durations, but more so in the 40ms duration (Chung and Bedell 1995). This reduction in VA with retinal image motion in “normal” observers was also demonstrated in two further studies (Chung and Bedell 1996, 1997). Chung and Bedell’s 1995 paper shows a larger crowding effect to Landolt C’s for people with nystagmus. Luminance has also been shown to have an effect on VA with regards to foveation. Longer foveation was associated

with improvements in VA at a luminance of 0.158 cd/m^2 and above, but had very little effect at a luminance of 0.0158 cd/m^2 and lower (Chung and Bedell 1997).

As described in section 2.6.1, foveation duration is gaze dependent, and so by association VA is also. Subjects with nystagmus have their best VA when using their null position (Yang et al. 2005). Yang et al. (2005) also used time restricted stimuli and found this to have a deleterious effect on VA. This has implications for those with nystagmus in the real world where various objects in the visual world are in motion, e.g. trying to see a bus number as the vehicle is moving. It would be expected that tasks such as this are more difficult for someone with nystagmus.

As described in section 2.6.2, some subjects with INS have a convergence null position. Although we would therefore expect improved VA for near tasks (Gamble 1934), no significant improvement is found even though nystagmus intensity is reduced (Hanson et al. 2006). This finding is attributed to a sensory limitation in their vision having a greater impact than the movements of the eyes themselves.

Recently, studies have been carried out on the progression of VA in children with INS (both idiopathic and associated with sensory deficits) (Weiss and Kelly 2007; Fu et al. 2011). Both studies indicated that children with nystagmus demonstrate a mildly reduced VA compared to normative data (Figure 2.11). Weiss and Kelly (2007) described a development in all children (idiopathic and those with sensory deficits) that mirrors but is lower than the normative curve. Fu et al. (2011) found this only for those children with idiopathic INS. However, Weiss and Kelly (2007) compiled their data from patient records and thus had actual longitudinal acuity development for individual patients whereas, Fu et al. (2011) had only cross-sectional data.

For people with INS, VA is also dependent on the orientation of the stimulus. Studies have shown that, for both those with idiopathic and INS associated with albinism, grating acuity is better for horizontal rather than vertical gratings. This has been attributed to the mainly horizontal movement of the eyes (Abadi and Sandikcioglu 1975; Loshin and Browning 1983; Bedell and Loshin 1991; Meiusi et al. 1993). Contradictory reports have been made concerning this effect for the Landolt C optotype. This will be discussed in more detail in chapter 4.

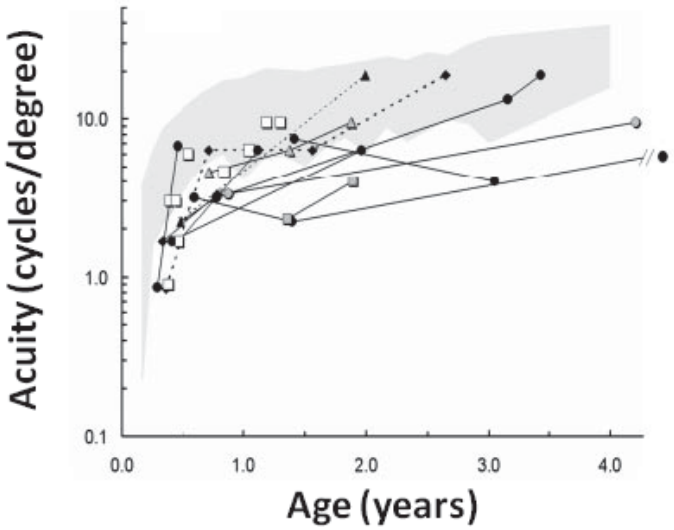

Figure 2.11: Figure showing the development of VA for children with idiopathic INS. Symbols connected with lines represents individual subjects. Shaded area represents the tolerance limits of "normal" binocular acuity (Weiss and Kelly 2007)

As well as the measurement of VA, investigators have designed predictor functions to provide an estimate of achievable VA for particular foveation parameters. The nystagmus acuity function (NAF) is described by Sheth et al. (1995) and is based on the length of foveation per second (Tf), the standard deviation of the position of the foveations from 0 (SD_P), and the standard deviation of the velocity of the eyes during foveation (SD_V).

A simplified version of the NAF is given in the NAFP in which the assumption is made that acuity has no correlation with the velocity of the eyes during foveation, and is thus only concerned with their position (Sheth et al. 1995).

These functions place very tight restrictions on the position criterion for foveation, requiring the eyes to be within ±0.5° of fixation. As we discussed in section 2.6.1, position is not always accurate and repeatable, many investigators having a more lenient position criterion for foveation (Cesarelli et al. 2000; Dell'Osso and Jacobs 2002; Bifulco et al. 2003; Pasquariello et al. 2009). Dell'Osso and Jacobs (2002) conducted an investigation (as described in section 2.6.1) in which both position and velocity restrictions were relaxed, and the outcomes of the eXpanded Nystagmus Acuity Function (NAFX) were compared to the previously described NAF. The relaxation of the position and velocity criteria for foveation results in the inclusion of all possible foveations. When using the NAFX, position and velocity criteria for the foveation window can be adjusted for each individual. Methods of applying these functions and variations on them are being developed regularly, with the most recent advancements aiming to produce automated methods of calculation (Tai et al. 2011).

The functions described above make the assumption that there is no underlying sensory defect and therefore provide an estimation of the potential VA achievable by an individual (Sheth et al. 1995; Dell'Osso and Jacobs 2002). However, as will be discussed later, there are other aspects of visual function in addition to VA that need to be addressed when considering people with INS.

From what we have discussed in this section and in section 2.6.1 regarding foveation, it can be hypothesized that, if those with nystagmus have a longer foveation period from early childhood, they have a better chance of developing good VA. However, if development of

good VA is obstructed an underlying amblyopia will be produced. If foveation is extended later in life, VA can only be as good as the underlying amblyopia. Nevertheless, many treatments for nystagmus aim at extending the foveation duration, and these treatments will be discussed in section 2.10.

2.8.2 Contrast Sensitivity (CS)

Burr and Ross (1982) conducted an investigation to explore the effects of retinal image motion on CS in subjects with no nystagmus or sensory defects. Sinusoidal gratings in the vertical orientation were moved across the retina at speeds of 1, 10, 100 and 800°/s. The threshold value was taken as the lowest contrast at which the drift of the grating could still be seen. As the velocity of the grating was increased, the shape of the contrast sensitivity function (CSF) was maintained but was shifted towards the lower spatial frequencies (Figure 2.12). Peak sensitivity to stationary gratings was found to be at 3 cycles per degree (c/deg). At a velocity of 100°/s, peak sensitivity was found at a spatial frequency of 0.06 c/deg, the level of sensitivity being maintained (Burr and Ross 1982).

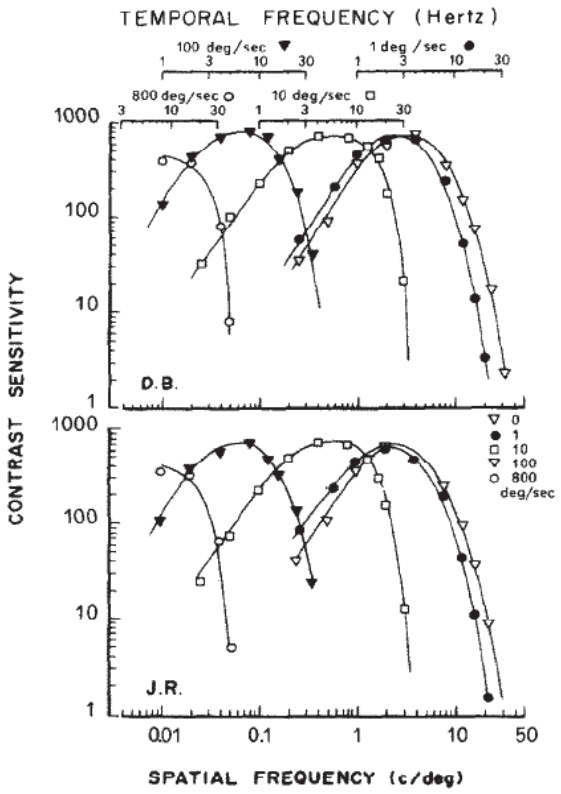

Figure 2.12: Shift in CS with increased retinal image motion (Burr and Ross 1982)

Dickinson and Abadi (1985) performed a similar investigation using a movement that simulated a nystagmus waveform. In this investigation, nystagmus waveform-like movements were generated using an oscilloscope on which vertically orientated sine wave gratings were presented. CS was unaffected for a spatial frequency of 1 c/deg. However, at frequencies greater than this, sensitivity was reduced (Dickinson and Abadi 1985). It was also noted that the type of nystagmus waveform simulated had an effect on sensitivity. P and P_{FS} waveforms were equal in their effects, whereas PC showed better relative CS especially at higher spatial frequencies. As amplitude or frequency increased (while the other was kept the same), so CS was reduced (Dickinson and Abadi 1985). Conversely, Abadi and King-Smith (1979) attempted to eliminate the effects of image motion in control subjects and people with nystagmus by using a 0.2ms presentation. Differences between horizontally and vertically orientated gratings were also evaluated. Subjects with nystagmus

had a reduced sensitivity to vertically orientated gratings by around 0.8 log units. A reduced sensitivity was also noticed when presentation was via the 0.2ms flash rather than unlimited. This was true for control subjects as well as those with nystagmus. For both the unlimited presentation and the 0.2ms presentation, contrast sensitivity was lower for those subjects with nystagmus compared with controls.

Contrast sensitivity has been measured in subjects with albinism (Loshin and Browning 1983) and also in those with INS (Hertle and Reese 2007). Loshin and Browning presented gratings on an oscilloscope and were able to alter orientation between vertical and horizontal. They found that all subjects showed reduced sensitivity to vertical gratings compared to horizontal. The peak spatial frequency for subjects in this investigation was found to be at 2 c/deg. The reduction in sensitivity for the vertically orientated gratings was attributed to the presence of horizontal nystagmus (Loshin and Browning 1983).

Hertle and Reese (2007) used a clinical measure of contrast sensitivity, the Functional Acuity Contrast Test (FACT). Reduced sensitivity was shown for INS subjects for spatial frequencies of greater than 1.5 c/deg. This is consistent with the studies reported above. This study concluded that high spatial frequency acuity testing, such as with Snellen acuity, may not give an adequate indication of the reduced visual function capabilities of someone with nystagmus (or other oculomotor instabilities) (Hertle and Reese 2007).

2.8.3 Refractive Error

Gamble (1934) reported the refractive errors of 65 patients with nystagmus. The range of spherical error was between -16DS and +11DS and the range of astigmatic errors was between Plano and 6DC. This study showed a high predominance of with the rule

astigmatism. Unfortunately, Gamble did not report whether these patients had idiopathic nystagmus or any associated ocular abnormalities.

Sampath and Bedell (2002) studied the distribution of refractive errors amongst a population of 46 persons with idiopathic INS and 19 persons with INS related to albinism. Their results indicated an average spherical equivalent refractive error of -1.37D (range -7.88 to +4.00D) in the idiopathic INS group and -0.65D (-13.75 to +7.30D) in the group with INS related to albinism. Although idiopathic INS was associated with more myopic refractive error, the difference was not significantly different. However, a significantly higher astigmatic error was reported for the group with albinism (mean 3.26DC) compared to those with idiopathic nystagmus (mean 1.88DC). With the rule astigmatism was more predominant in both groups (83%). Sampath and Bedell reported that the distribution of refractive errors fell outside the normative curves for both adolescent and adult patients (Sampath and Bedell 2002) (Figure 2.13).

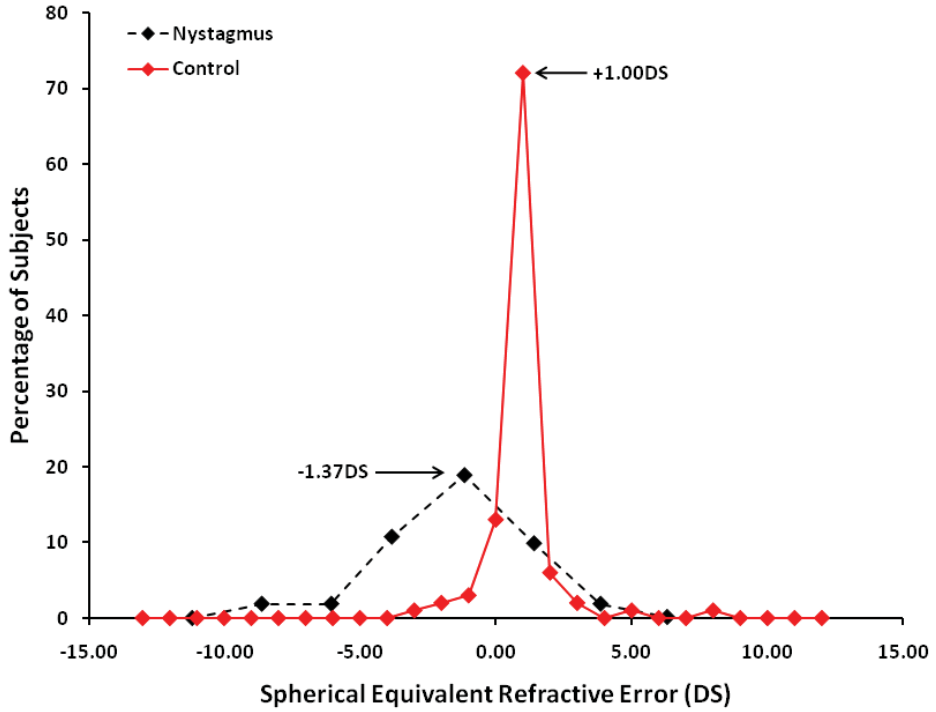

Figure 2.13: Distribution of refractive error for subjects with idiopathic INS (aged 10 to 43) and control subjects (aged 4 to 18). Nystagmus data from Sampath and Bedell (2002), control data from McClelland (2004)

This wide variation shows that there is no systematic relationship between nystagmus and either hypermetropia or myopia. However, Sampath and Bedell indicate that the shift away from the normative curve is indicative of poor emmetropization. Anderson et al. (2004), reporting on the use of spectacles in albinism, found spherical errors of between -12.25 and +7.25DS and astigmatic errors of between Plano and 6.75DC.

As mentioned previously, there is a predominance of with the rule astigmatism in patients with nystagmus. Wang et al. (2010) investigated the change in astigmatic refractive error in the first 8 years of life. It was found that both the prevalence and the size of the astigmatic error increased with age. Those with INS associated with albinism displayed a significantly higher mean astigmatic error (with the rule) compared to the idiopathic group. The higher prevalence of with the rule astigmatism in subjects with nystagmus is thought to be the result of the mechanical action of the lids on the cornea. This is, in part, confirmed by Dickinson and Abadi (1984), who measured corneal topography in subjects with INS and found the astigmatism present in these subjects to be mainly corneal in origin.

2.9 How "Stress" Affects Nystagmus

Before we describe the literature regarding the effects of stress on nystagmus, it is necessary to give a brief overview of the relevant terms "arousal", "stress", "anxiety" and "fear".

2.9.1 What are Arousal, Stress, Anxiety and Fear?

Stress is an extremely difficult term to define. Jones and Bright (2001) indicate that the difficulty lies in separating common uses of the term from experimental uses. People use the term stress to describe many things. For example, a particular activity or job can be

considered stressful. In fact, in this example, we are actually describing a stressor (i.e. the job or activity) (Jones and Bright 2001).

Subconsciously, humans analyse situations, categorising them as either dangerous or safe. Feelings are described as the "conscious subjective experience that corresponds to an emotion"(Longstaff 2005a). From these descriptions, we can now see that the term stress is used to describe emotions, feelings, and even the situations that elicit these. Ursin et al. (2004) suggest that stress has four "aspects": the stress stimulus, the stress experience, the stress response, and the feedback of this response. The stress stimulus, or stressor, is generally defined as something that will trigger the further three stages. The stress experience is the feeling of anxiety, the stress response (arousal) is the body's physiological response to the stimulus, and the feedback is a positive feedback loop that manifests as the "experience of the stress response," which in fact increases the feeling of stress (Ursin and Eriksen 2004).

The literature based on the clinical examination of stress and anxiety indicates that stress is the term usually linked to the situation or external event which brings about the stressful feeling. In other words, the term stress is used in connection with the "stressor" (Spielberger 1975). It therefore becomes clear that a more useful term might be anxiety or fear. Anxiety is the feeling of uneasiness produced by an unknown stimulus, vague event (Rachman 1998) or dangerous situation (Spielberger 1975). This same feeling, when linked to a known stimulus, is termed "fear" (Rachman 1998). The "physiological arousal" linked to fear characteristically has a sudden onset and is reduced when the threat is removed. This is differentiated from anxiety, in which the source of the feelings is more uncertain. Stress, anxiety and fear all have effects on the body, the body's physiological response to a stressor

being termed “arousal” (Evans 1976; Kirsch and Geer 1988). On first contact with the stressor, this arousal is the result of excitation of the sympathetic nervous system (Burchfield 1979).

2.9.2 How Does Stress Affect the Body?

The response to stress, anxiety and fear is adaptive in nature (Ursin and Eriksen 2004). The arousal caused by a stressor triggers an organism to eliminate the source of the arousal, mediated by the feedback loop mentioned earlier. If the source cannot be eliminated, then a sustained response occurs (Ursin and Eriksen 2004). The changes in the body to eliminate the stressor are, taken together, what is known as the “fight or flight” response (Motzer and Hertig 2004). In this response, physiological changes occur as a result of stimulation of the sympathetic nervous system (Burchfield 1979). This causes an increase in the rate of cardiac output and respiration, redirection of blood flow and the use of stored energy (Burchfield 1979; Motzer and Hertig 2004). In the “fight or flight” response, alertness, arousal (from the release of adrenalin) (Jones and Bright 2001) and attention are all increased, with feeding and sexual behaviour reduced (Motzer and Hertig 2004). Similar responses are said to occur with anxiety and fear, namely increased heart rate, increased respiration, sweating and muscular tension (Spielberger 1975).

All of the above responses prepare the body for action. The increase in the rate of blood flow (heart rate) means that more oxygenated blood is supplied to the skeletal muscles (Burchfield 1979; Jones and Bright 2001; Motzer and Hertig 2004). This increase in blood supply is essential for quick action. The muscles have increased tone and tension during this type of response, which allows them to act not only quickly but strongly (Misslin 2003). As well as an increased heart rate, the arterial vessels constrict. This increases blood pressure

and also means that blood moves faster around the body (Jones and Bright 2001). This type of response from the cardiovascular system can, however, have adverse consequences if repeatedly occurring as a result of day to day activities. Possible consequences in people include atherosclerosis, heart attack and even stroke (Jones and Bright 2001; Carroll et al. 2007; Kirchhof et al. 2007).

It has been mentioned above that the stress response increases sweating. In extreme cases, this can aid in cooling the body when involved in physical activity (Motzer and Hertig 2004). The main sweat glands involved in stress are the eccrine glands, which are controlled by the sympathetic nervous system. These differ from the other type of sweat gland (apocrine) as they excrete onto the surface of the epidermis as opposed to excreting into hair follicles (Tortora and Grabowski 2003). The eccrine glands are distributed across the surface of the skin but are found in especially large numbers in the forehead, palms of the hands and soles of the feet. The number of glands in the palms of the hands can be as high as 3000 per square inch (Tortora and Grabowski 2003). Normally, in the absence of a stressor, the palms of the hands and the soles of the feet are the last to produce sweat, but under conditions of emotional stress, they are the first (Tortora and Grabowski 2003). It is because of this that measuring electrodermal activity allows us to monitor a subject's state of arousal/stress (Dawson et al. 2000). The technique of measuring electrodermal activity will be discussed in more detail in chapter 5.

As well as having physiological effects, stress in its extreme form can have psychological effects on people. Those who are constantly under a lot of stress can sometimes suffer with depression (Jones and Bright 2001; Carroll et al. 2007). The extremes of stress can also lead

to panic and anxiety disorders, which can be very debilitating to people's lives (Spielberger 1975; Rachman 1998; Jones and Bright 2001).

2.9.3 Current Knowledge of the Effects of Stress on Nystagmus

It is often reported anecdotally that stress has a deleterious effect on vision in people with nystagmus (Abel 2006; Khanna and Dell'Osso 2006). In 1986, Abadi and Dickinson, in their investigation into waveform characteristics in nystagmus, made the observation that, as one subject became more relaxed, the amplitude of their eye movements became less and foveation became longer and more accurate (Abadi and Dickinson 1986). However, until recently, the effects of stress on nystagmus waveform had not been quantatively measured.

Early studies by Dell'Osso (Dell'Osso 1973) indicated that fixation attempt (i.e. to hold fixation for longer) caused an increase in the intensity of nystagmus, and this has since been supported by others (Abadi and Dickinson 1986; Abadi and Bjerre 2002). Visual demand, or "effort to see", had also been suggested as an exacerbating factor but had never been quantitatively measured (Abadi and Dickinson 1986). Two studies have since aimed to quantify this, with differing results. Tkalcevic and Abel (2005) found that increased visual demand ("effort to see") had no effect on intensity and foveation duration of the waveforms. On the other hand, Wiggins et al. (2007) demonstrated an adaptation of the nystagmus waveform to increased visual demand, with intensity decreasing and extended foveation.

Both Tkalcevic and Abel (2005) and Wiggins et al. (2007) attribute their findings to visual demand in the absence of stress. Wiggins et al. reported that stress was minimal in their experimental setup, with subjects having unlimited viewing time for optotypes. It was

concluded that “task demand” is the factor that may have a detrimental effect on the nystagmus waveform (Wiggins et al. 2007). Tkalcevic and Abel suggest that motivating people to do well on a visual task (e.g. to achieve VA good enough to drive) would introduce a psychological stress, which they expect would have a deleterious effect on the nystagmus waveform and hence VA.

Cham et al. (2008a) performed VA measurements on subjects with INS under three different conditions: unrestricted viewing, restricted viewing and reward manipulation. During the unrestricted viewing, each stimulus presentation was visible for an unlimited time until the subject responded. During the restricted viewing task, the duration of the presentation was altered depending on LogMAR VA. Mental arithmetic was also performed by subjects during this task. The reward manipulation task was the same in its design as the restricted viewing task with a monetary reward/punishment applied. For every correct answer, the subject was awarded $0.50, and for every incorrect answer, $1.00 was deducted. The results showed an increase in waveform intensity during the restricted and reward manipulation tasks, as well as a reduction in foveation. VA in this study was measured using optotypes with “slightly blurred edges” in order to enhance the stress of the task. As the task was modified to increase its difficulty, a true measurement of the subjects VA could not be determined, and therefore, no definite conclusions can be drawn as to the effects of stress on VA (Cham et al. 2008a). The study conducted by Cham et al. (2008a) confirms previous observations of the effects of stress on nystagmus waveform, however further investigation is need to investigate the effects of stress on visual function. A more detailed discussion of the study by Cham et al. (2008a) can be found in chapter 6.

2.10 Treatment

Many different treatments have been proposed for nystagmus, ranging from medication to extra-ocular muscle surgery. These treatments do not, however, cure nystagmus completely but merely aim to alter the nystagmus movements and/or null point in order to improve the vision of those with the condition. Many treatments attempt to increase the foveation period of the nystagmus waveform, based on the link this is reported to have with VA. Other treatments are "cosmetic", used, for example, to reduce or eliminate abnormal head posture as a result of an eccentric null point.

2.10.1 Non-Surgical Treatments

Non-surgical treatments for nystagmus can be split into pharmacological treatment, treatment with optical devices, and alternative therapies.

2.10.1.1 Pharmacological

Pharmacological methods vary greatly depending on the type of nystagmus. For acquired nystagmus, treatment of the underlying condition is often necessary (for example, in nystagmus associated with vertigo). In the treatment of an acquired pendular nystagmus associated with multiple sclerosis and optic neuritis, Liao (2007) found that pregabalin produced a reduction in the nystagmus as opposed to the more widely used drugs in nystagmus treatment.

In INS, memantine and gabapentin have been found to significantly reduce nystagmus intensity and increase the duration of the foveation period in a randomised control trial (RCT) (McLean et al. 2007). McLean et al. also note an average 0.15 LogMAR improvement

in VA in those patients taking memantine, and a 0.09 LogMAR improvement in VA for gabapentin (McLean et al. 2007). The exact mode of action by which these drugs modify nystagmus is unknown.

2.10.1.2 Optical Devices

With any treatment of nystagmus, it is important to correct the refractive error. Once the appropriate refraction is in place, various approaches have been employed to increase the duration of the foveation period. Many techniques involve the use of prisms so that the null position can be utilised without having to resort to the use of an abnormal head posture (Abel 2006). This is only practical in those patients with a null position close to the primary position. Large gaze angles require large prisms to move the image, thus reducing image quality and resulting in cosmetically unacceptable spectacles (Abel 2006). Base out prisms in both eyes can be adopted in order to take advantage of a convergence null position (Yaniglos et al. 2002). The use of 7^{Δ} base out prism has been shown to be effective and, for pre-presbyopic patients, should be combined with a -1.00DS lens over the prescription in order to counteract the accommodation produced by such convergence (Dell'Osso 2002; Evans 2007).

Contact lenses have also been noted to be preferable to spectacles in improving VA (Allen and Davies 1983; Biousse et al. 2004). Allen and Davies (1983) showed improvement of VA in 7 out of 8 subjects with contact lenses compared to spectacles, 4 improving by 3 lines on the Snellen chart. However, Biousse et al. (2004) fitted contact lenses to four patients with INS and found peak velocity and amplitude to reduce, and percentage foveation time to increase, for only one subject. They also noted no improvement with two subjects, and worsening in another. One hypothesis for the reported dampening of nystagmus during

contact lens wear is tactile feedback of the lens on the eye as it moves (Allen and Davies 1983; Abel 2006). However, this was not found significant in the study by Biousse et al. (2004). Dell'Osso et al. (1988) investigated this in one patient by using anaesthetic. It was found that removing the tactile feedback with anaesthetic had little effect on the nystagmus waveform. The improvement in VA has been linked to the improved optics contact lenses provide as patients are able to look through the optical centre of the lenses for a longer time (Allen and Davies 1983; Dell'Osso et al. 1988; Biousse et al. 2004). The small number of subjects used in previous research, and the contradictory results found in the literature on the effect of contact lenses on nystagmus, means that there is insufficient evidence for their use therapeutically.

2.10.1.3 Alternative Therapies

Several alternative therapies have also been suggested. Evans et al. (1998) conducted a randomised, double masked placebo controlled trial in order to investigate the effects of intermittent photic stimulation (IPS) on nystagmus. This technique was first proposed by Mallett (1983) and involves the patient carrying out detailed visual tasks of back illuminated material with a red spot flickering at 4Hz. Subjects fixated an opaque disc on a flash gun, which was then flashed at 50cm. Patients were then asked to read detailed tasks on the IPS whilst instructed to keep the after image as still as possible. However, this study showed no improvement of visual acuity with this type of treatment, although an improvement of contrast sensitivity to vertical gratings was found (Evans et al. 1998).

Blekher et al. (1998) have shown that some people with nystagmus demonstrate a reduction in amplitude and increased foveation duration with acupuncture treatment. Four out of six subjects demonstrated longer foveation periods during treatment. Three of these

subjects continued to demonstrate a significantly longer foveation once the needles had been removed (Blekher et al. 1998).

2.10.2 Surgical Treatment

Many surgical procedures have been employed in the treatment of nystagmus, as summarised in table 2.2.

Lee (2002) found that rectus muscle recession is the commonest form of surgery used in nystagmus, with resection being the most common surgery to strengthen the muscles.

Procedure	Description
Recession	Muscles (usually horizontal recti) removed and repositioned 5-7mm posterior to the original position
Resection	Muscles (usually horizontal recti) shortened by removing a 5-8mm section.
Kestenbaum	Recession of the muscles whose action is in the direction of the head turn, resection of the antagonist muscles
Anderson	Recession of the two yoked muscles involved in the slow phase of the nystagmus waveform
Artificial divergence	Resection of the two lateral rectus muscles
Maximum recession	Recession of all four rectus muscles
Tenotomy	Detachment of the muscle, dissection of the perimuscular fascia and reattachment at the same position

Table 2.2: Overview of the surgical treatments available for nystagmus

The Kestenbaum procedure is used in patients with nystagmus who make use of an eccentric null position, with an abnormal head posture (Calhoun and Harley 1973; Leigh and Rucker 1999; Lee 2002). The Anderson procedure is similar to the Kestenbaum but is only concerned with the muscles involved in the slow phase of the nystagmus (Anderson 1953;

Gupta et al. 2006), the fast phase being seen as a natural saccadic response (Reinecke 1997). These procedures can be combined into one, the Anderson-Kestenbaum procedure, which involves the recessions of the muscles being performed as in the Anderson procedure and resection as in the Kestenbaum procedure (Taylor and Jesse 1987).

Artificial divergence surgery aims to take advantage of the presence of a convergence null (Graf et al. 2001; Lee 2002; Khanna and Dell'Osso 2006). When the eyes are in their primary position, there is the effect of fusional convergence. Artificial divergence gives the best results with the minimum amount of surgery (Graf et al. 2001; Lee 2002). Studies have shown that maximum recession results in increased VA, as well as an improvement in the nystagmus itself (Hertle et al. 2004a).

The most recent advancement in surgery for the treatment of nystagmus is tenotomy of the rectus muscles. This was first proposed hypothetically by Dell'Osso (1998). The hypothesis was based on the observation that, although predominantly used to alleviate AHP, the Anderson-Kestenbaum procedure results in a reduced intensity nystagmus, this reduced intensity being linked to changes in the extraocular muscle and tendons following the procedure (Dell'Osso 1998). Damped nystagmus, an increase in the maintenance of fixation and a longer period of fixation postoperatively were all demonstrated in a pilot study of five subjects, with improvement of NAFX score in 4 out of 5 patients. The same 4 patients also showed improvements in binocular VA (Hertle et al. 2004b). Recently, combination of tenotomy with recession has been shown to improve AHP, foveation duration, and binocular VA (Hertle et al. 2011). The exact mode of action of tenotomy is not fully understood. It has been proposed that a possible explanation of the changes seen following

tenotomy is a change in the control of muscle tension, and possibly proprioception (Wang et al. 2006).

2.11 Summary

It can be seen when viewing the literature on nystagmus that there are many varied ways of analysing, classifying and treating the condition. The important waveform factors of amplitude, frequency, and intensity have been introduced, as well as the importance of foveation and the null position with regards to visual function. As discussed, many treatments aim to increase the foveation duration later in life. However, as this is generally performed later in life, i.e. once the patient has left the plastic period of vision, this does not necessarily improve VA significantly.

It has been suggested that the presence of stress has a deleterious effect on the nystagmus waveform and foveation duration (Abadi and Dickinson 1986; Tkalcevic and Abel 2005; Wiggins et al. 2007). Although this has recently been confirmed, the effects on VA remain unclear (Cham et al. 2008a). The studies described in this thesis aim to investigate the effects of stress on the VA of people with nystagmus, using robust psychophysical methods and simultaneous eye movement recording.

Chapter 3: Subject Recruitment and Methods for Measuring Visual Function

This chapter will outline the recruitment of subjects and the various methods available for the measurement of visual function.

3.1 Subject Recruitment

Subjects (over the age of 18) with nystagmus were primarily recruited from the Research Unit for Nystagmus (R.U.N.) cohort. The cohort was established in 2000 via recruitment through the Nystagmus Network (NN) website (www.nystagmusnet.org) and its newsletter. In 2007, following an update, the cohort consisted of 31 volunteers. Throughout the duration of the current studies, a further 7 volunteers were added, again via advertisements on the NN website and in the newsletter. Following a questionnaire survey (sent out to the NN newsletter readership, see chapter 7), 5 respondents agreed to take part in our current studies with a further 76 requesting to be kept informed of future research. The cohort size currently stands at 119 volunteers, who have registered an interest in taking part in nystagmus research. The majority of volunteers are those with idiopathic nystagmus, but some have manifest latent nystagmus or nystagmus associated with other conditions, namely albinism, ocular albinism, and rod monochromatism (self reported information). Subjects with ocular conditions other than idiopathic INS, or INS associated with albinism/ocular albinism were excluded from the current studies. The clinical information for each experimental subject is shown in Appendix I.

Control subjects comprised staff and students at the School of Optometry and Vision Sciences, Cardiff University, as well as friends and family of the lead researcher. Whenever

possible, control subjects were age matched to those with nystagmus. Clinical information for all control subjects can be found in Appendix II.

As well as the exclusion criteria described above for those with nystagmus, further exclusion criteria applied to both those with nystagmus and control subjects. Subjects with a recent history of migraine and/or epilepsy were excluded from participation in the investigation into the effects of stress on visual function (chapter 6), as stress has been linked to the onset of both of these conditions (Betts 1992; Holm et al. 1997). The use of the TENS machine (chapters 5 and 6) also introduced additional exclusion criteria. The use of a TENS machine is not recommended if subjects (Want 2007):

- May be pregnant
- Suffer with leprosy
- Suffer with chronic alcoholism
- Suffer with skin disease
- Have any heart conditions
- Have a pacemaker fitted

All investigations were carried out in accordance with the Declaration of Helsinki (2008b) and all subjects gave written consent after reading an information sheet for each investigation (Appendix III). Opportunity was given for subjects to ask questions, and subjects were informed that they were free to withdraw from the investigation at any time. Ethical approval for all investigations was granted by the School of Optometry and Vision Sciences, Cardiff University, Human Research Ethics Committee.

Prior to investigation, all subjects had an ocular examination (conducted by the lead researcher, an optometrist) which included a brief history, VA measurement, retinoscopy, and ophthalmoscopy. Subjects wore their habitual Rx during the investigations, unless a difference of greater than ±0.50DS was found on retinoscopy (Rosenfield and Chiu 1995), when the new correction was used. Ophthalmoscopy was performed in order to identify any underlying pathology which might cause a worsening of VA (subjects with ocular pathology were excluded).

3.2 Measuring Visual Acuity (VA)

For the experiments discussed in this thesis, it was essential to obtain accurate measurements of VA in order to note any changes in a subject's perception arising from changes in the orientation of the stimulus or to changes in the waveform of their nystagmus eye movements.

To measure VA in the laboratory setting, a computerised method was used. In order to obtain accurate VA measurements, a computer-based psychophysical procedure must use the lowest number of stimulus presentations, require only basic responses on the part of the patient, and keep psychological bias to a minimum (Corliss and Norton 2002). There are a number of different psychophysical methods that may be used to estimate VA. These are based on the three classical psychophysical methods (Gescheider 1997), which are:

Method of Constant Stimuli - This method is considered to be the most accurate of the psychophysical tests. The researcher chooses a range of stimuli for which the largest are above threshold and the smallest below (Gescheider 1997; Corliss and Norton 2002). The stimuli are presented repeatedly in a random order, and a "psychometric function" is

constructed showing the percentage of positive responses (i.e. subject perceived stimulus) for each stimulus (Gescheider 1997). Threshold is normally taken as the stimulus which the subject was able to see 50% of the time (Corliss and Norton 2002). The principal limitation of this method is that it is time consuming (Gescheider 1997).

Method of Adjustment - This method differs from the other psychophysical methods in that the observer is given control of the size/intensity of the stimulus (Gescheider 1997; Corliss and Norton 2002). The stimulus is set to begin either far above or below the subject's expected threshold. The subject then reduces/increases the stimulus until either it just disappears or until they can just see it. The threshold is taken as the average of these repeated values (Gescheider 1997; Corliss and Norton 2002). This is considered the least accurate of the classical methods as observer bias is more difficult to control (Gescheider 1997; Corliss and Norton 2002).

Method of Limits - This method is the most commonly used of the psychophysical tests (Gescheider 1997; Corliss and Norton 2002). Similar to the Method of Constant Stimuli, this approach involves the researcher choosing a set of stimuli that range from supra- to sub-threshold. Stimuli are presented in an ascending or descending order. If presented in ascending order first, they are then presented in descending order. Subjects give a yes or no response and continue the test until they provide a set number of consecutive opposite responses, i.e. for a descending trial the responses change from YES to NO, and for an ascending trial the answers change from NO to YES (Corliss and Norton 2002). A trial in the opposite direction is then started. This is repeated a number of times. Threshold is taken as the average of the acuities at which the observer response changed (Gescheider 1997; Corliss and Norton 2002). This method does have limitations, in that for ascending and

descending trials, subjects may pre-empt the change in stimulus from sub- to supra-threshold. A commonly used method to correct for this is the staircase procedure (Cornsweet 1962), which is the method adopted for the studies described in this thesis.

There are a number of limitations to psychophysical tests because of subject bias. For example, subjects may say that they can see a stimulus that is actually sub-threshold, in order to do well. The converse of this is also true. The most accurate way of controlling this bias is to use alternative forced-choice procedures (Corliss and Norton 2002). The method was first described by Blackwell (1953; cited in Gescheider 1997) and forces the subject to make a choice between two or more possible responses. The benefit of the forced choice is that it removes the subject's bias from the investigation by predetermining the guessing rate (Gescheider 1997; Corliss and Norton 2002):

$$\text{True \% of correct responses} = \frac{(\text{Observed rate of correct responses} - \text{Guessing rate})}{(1 - \text{Guessing rate})} x100$$

A two alternative forced choice procedure would have a guessing rate of 0.5. From the above equation, taken from Corliss and Norton (2002), a 75% correct response would indicate that the true percentage of correct responses is 50%. All of the studies described in this thesis used a two-alternative forced-choice (2AFC) staircase procedure.

Another way of increasing the accuracy of the staircase is to employ the use of the up-down transformed response (UDTR), which was first developed by Wetherill and Levitt (1965). For this procedure, the direction of the staircase is altered based on a preset criterion. For example, if the staircase procedure starts by descending, the observer is required to provide three correct responses before the stimulus will become smaller. One incorrect response results in the staircase ascending (increasing stimulus size), until three correct responses are

once again given and the descending staircase continues. The staircase switching from descending to ascending is termed a "reversal". Threshold is taken as the average of a number of reversals (Corliss and Norton 2002). For the studies described in this thesis, the threshold VA was calculated as the mean of the last six reversals. This is in accordance with García-Pérez (1998; 2000). The UDTR procedure requires a higher percentage of correct responses, making it more accurate (Wetherill and Levitt 1965; Gescheider 1997). The percentage correct response required for a threshold measurement is given by the equation:

$$X = n\sqrt{y}$$

(X = probability value, n = Number of correct responses needed,
y = chance performance level)

The studies in this thesis used a 3 up / 1 down procedure, which sets the threshold at the level at which 79% of the stimuli are seen correctly.

3.3 Eye Tracking

Eye movement recordings allow nystagmus waveforms (i.e. eye position against time) to be quantified in terms of amplitude, frequency and intensity. This is important so that we can identify any changes in waveform under experimental conditions, namely stress in the case of this study. The measure of foveation duration is particularly useful both clinically and experimentally. Clinically this measure can, for example, allow us to make predictions about the development of a child's VA in the presence of nystagmus. As discussed in section 2.4.1, a longer foveation period is generally associated with better VA (Abadi and Worfolk 1989). Experimentally, this measure allows estimations of possible improvement or degradation of VA with waveform changes. The use of eye tracking to obtain the above information is also

useful when looking at clinical outcomes. By using amplitude, frequency and foveation information, outcomes of surgical, medical and optical treatments for nystagmus can be measured in more quantified terms rather than relying purely on observation, which is subject to observer bias.

There are many eye trackers available today, but all can be classified as belonging to one of four generations. The first generation comprises the Scleral Search Coil (SSC) technique and Electro-Oculography (EOG). The second generation is made up of Photo and Video-Oculography systems. For the third and fourth generations, the eye trackers use two different identifying characteristics of the eye, for example, the first Purkinje image and the relative pupil size. The fourth generation simply uses digital rather than analogue systems to accomplish this (Duchowski 2007).

3.3.1 Scleral Search Coil (SSC)

The gold standard of eye trackers is the SSC, which works on the basis of Faraday's Law (Williams 1967). This system consists of a wire coil embedded in a semi-scleral contact lens (Figure 3.1).

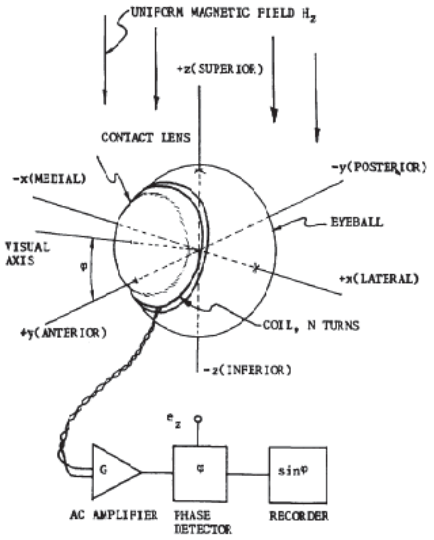

Figure 3.1: Diagram of the wire coils placed into a scleral lens (Robinson 1963)

The subject wears the contact lens and sits with their upper body inside a frame (generally 2ft x 2ft x 2ft) in which are embedded coils that produce a magnetic field (Robinson 1963). As the eye moves through the magnetic field, a current is induced in the coil (Robinson 1963). Robinson showed that using one coil to produce a magnetic field in one plane can give us one measure of eye movement, i.e. horizontal, vertical or rotational. He therefore proposed the use of three coils within the contact lens and three magnetic field coils in order to measure the movements of the eyes around all three axes simultaneously (Robinson 1963). The SSC is the highest resolution eye tracker available, with an accuracy of 5-10 seconds of arc (0.001° – 0.003°) and a temporal frequency of 1000Hz (Robinson 1963). This extreme degree of accuracy is over only a limited range of ±5° (Duchowski 2007), although studies report this method to be highly accurate and have a linear (or close to linear) range of ±20° (Collewijn et al. 1975; Yee et al. 1985). The contact lens of the SSC has been found to have adverse (albeit usually transient) effects on the eye, which include hyperaemia of the bulbar conjunctiva, corneal staining, and increased IOP. Another important factor noted, which affects the choice of this eye tracker for the research to be discussed in this thesis, is that VA is reduced (Irving et al. 2003).

3.3.2 Electro-Oculography (EOG)

EOG uses the standing (corneo-fundal) potential of the eyes in order to track their movements. This potential is generated from the difference between the relatively high metabolism of the pigment epithelium and the lower metabolism of the cornea, the retina demonstrating a more negative potential compared to the cornea, thus the eye acts as a dipole (Mowrer et al. 1935; Arden et al. 1962).

In order to record eye movements using EOG, electrodes are placed on the face around the eyes. Changes in potential are only recorded in the plane in which the electrodes are placed, and not at 90° to their positioning (Mowrer et al. 1935). For example, if the electrodes are placed at the nasal and temporal canthus of the eyes, horizontal movements would be recorded but not vertical. In order to measure both horizontal and vertical eye movements, electrodes need to be placed both horizontally and vertically, i.e. the electrodes placed directly above and below the eyes. A reference electrode is placed on the forehead. An example of positioning of the electrodes for measuring horizontal movements is shown in figure 3.2.

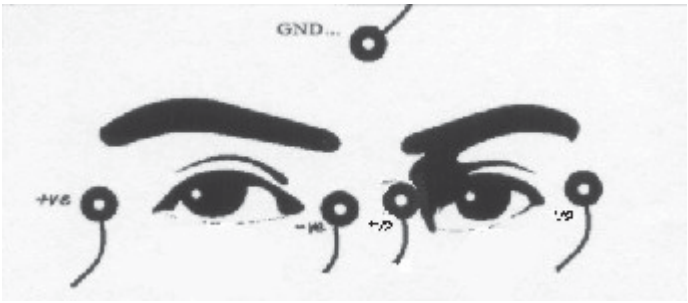

Figure 3.2: Diagram showing the positioning of electrode for EOG recording of horizontal eye movements. Taken from http://www.wch.sa.gov.au/services/az/divisions/paedm/neurology/electro.html (2009)

For simplicity, let us think of the right eye only. As the eye moves to the right, the more positive cornea moves closer to the temporally placed electrode and thus the recorded potential becomes more positive. At the same time, the more negative retina has moved closer to the nasal electrode and thus the recorded potential becomes more negative. The EOG records potentials in the range of 15 – 200 μV (Duchowski 2007). The accuracy of EOG recordings using skin electrodes is around ±1.5 - 2°, and eye movements can be recorded with this technique up to ±70°, although linearity is compromised above ±30° (Young and Sheena 1975a). However, the standing potential of the eyes is not constant between subjects, and can vary from one eye to the other in the same subject. The measurement is

therefore a comparative measurement of the change in the potential measured by the electrodes with respect to the standing potential. The corneo-retinal potential is also prone to change with respect to light and dark adaptation, alertness and diurnal variations (Young and Sheena 1975a). Because of these fluctuations, regular recalibration is necessary, making it unsuitable for lengthy recordings. The temporal frequency of the EOG is limited only by the equipment used. EOG has the advantage that it is not as invasive as the SSC method and is well tolerated by children as well as adults of all ages.

3.3.3 Photo and Video-Oculography

Photo and Video Oculography encompass both the second, third and fourth generations of eye trackers. Photos or videos are taken of the eyes as they move, and these systems measure the position of distinguishing features of the eyes such as corneal reflections, the Purkinje images, the limbus and/or the pupil (Young and Sheena 1975a, b). In second generation instruments, these outputs were analyzed by hand, the analyst looking through the data frame by frame or photograph by photograph. The position of the eyes over time could then be plotted. The temporal frequency of the instrument is dependent on the temporal sampling frequency of the video device (Duchowski 2007).

The third and fourth generations combine two identifying properties of the eye, e.g. corneal reflections and the relative size of the pupil. The combination of two features such as these allows measurement of the “point of regard”, i.e. where the subject is fixating rather than the position of the eye in the orbit. The system uses these two properties to separate translational movements from rotational (Young and Sheena 1975a). The difference between the third and fourth generations is that the fourth uses digital imaging systems rather than analogue.

3.3.4 IRIS

The eye tracker chosen for the research described in this thesis is the Skalar IRIS system (Skalar Medical BV, Delft, The Netherlands). The IRIS is a second generation eye tracker, which works on the basis that there is a difference in the reflected luminance of infrared light between the sclera and iris. The IRIS consists of two eye pieces on a headband, as shown in figure 3.3. As the system is head mounted, it allows subjects a little more freedom of movement. The two eye pieces are also individually adjustable, allowing both eyes to be calibrated separately and as accurately as possible. Each eye piece is complete with a two cell ocular (Figure 3.3), which allows subjects to use their habitual spectacle correction. These physical features of the system made it ideal for the research described here; it also has many technical benefits, which will be detailed next.

Figure 3.3: The IRIS headset. Left: head band and oculars; Right: close up of the left ocular with two cell lens holder in place

The IRIS system was first described by Reulen (1988), and consists of a head mounted eye tracker, which has 9 infrared light emitting diodes (LED's) positioned above the eye and 9 infrared light sensitive phototransistors positioned below the eye (Figure 3.4) (Reulen et al. 1988). As IR light is present in natural and artificial lighting, the LED's emit chopped IR light so as to minimise any interference this may cause. The chopped IR light is emitted with a frequency of 2.5 kHz, driven by a 50mA current.

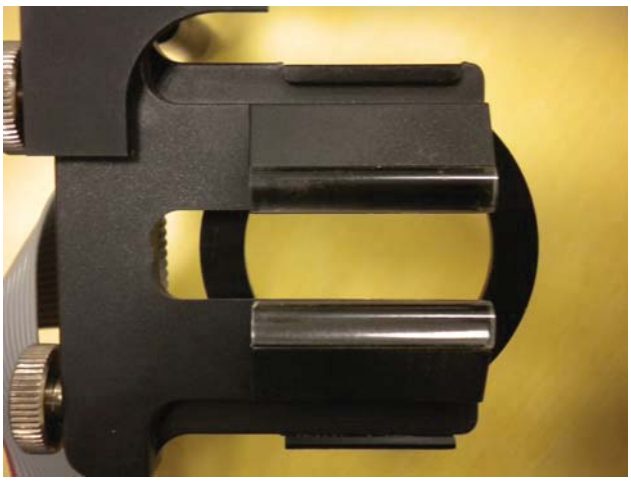

Figure 3.4: Picture of the LED's (top) and light sensitive phototransistors (bottom) at the back of the left eyepiece

The eye movement signal, which is generated by the IRIS, is first band pass filtered (centre frequency 2.5kHz, roll of 12dB/Octave), and multiplied by the square wave signal. It is then low-pass filtered (DC-100Hz; -3dB) before finally being amplified (Reulen et al. 1988). This is demonstrated in Figure 3.5.

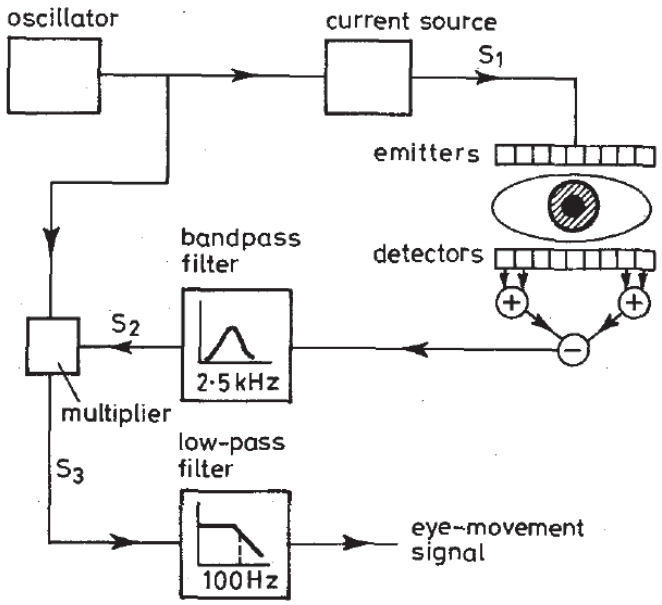

Figure 3.5: Schematic representation of signal acquisition from the IRIS system (Reulen et al. 1988)

The IRIS system measures both the nasal and temporal limbal margins with a temporal frequency of 1000Hz and a high spatial resolution of approximately 0.1°. The IRIS is linear (to within 3%) over a range of ±30° (Reulen et al. 1988). These features make the IRIS ideal for nystagmus research. The large speeds, at which the eyes can move, particularly during resets, require a high sampling (temporal) frequency for detailed analysis. As discussed in section 2.4.2, people with nystagmus demonstrate a large range of null positions (±40°, the majority falling within ±20°) (Abadi and Bjerre 2002). This requires that the recordings have linearity over a large range of eye position. The only drawback of the IRIS system is that it is only possible to measure either horizontal **or** vertical eye movements at any one time. However, as the eye movements in INS are predominantly horizontal, this is only a minor drawback and has minimal, if any, impact on these experiments. A discussion of the calibration procedure for the IRIS system can be found in Chapter 6.

Chapter 4: The Effects of Stimulus Orientation on Visual Acuity in Nystagmus

4.1 Introduction

As discussed in section 2.6.1, nystagmus has a deleterious effect on visual acuity. For practical purposes the target of choice for VA measurements was an optotype. The question then arises as to whether the orientation of the target will influence the acuity score. Several previous studies have been based on the hypothesis that, due to the predominantly horizontal eye movements, VA will be better for stimuli presented horizontally compared to those presented vertically (Abadi and Sandikcioglu 1975; Loshin and Browning 1983; Bedell and Loshin 1991; Meiusi et al. 1993).

Consistent with this view, significant improvements in VA for gratings oriented horizontally compared to vertically have been reported. Abadi and Sandikcioglu (1975) showed this difference for subjects with idiopathic nystagmus. Loshin and Browning (1983) reported similar findings in subjects with nystagmus associated with albinism, and Bedell and Loshin (1991) and Meiusi et al. (1993) showed this effect in both subjects with INS and nystagmus associated with albinism. Control groups in all of these studies showed no significant difference between horizontally and vertically oriented gratings.

When considering stimuli other than gratings, the literature is less clear. The Tumbling E has been used as a visual stimulus in previous research on people with nystagmus (Hertle et al. 2002); however, this stimulus was only presented in one orientation (with the limbs horizontal). To our knowledge, no investigation has been undertaken of the differences

between horizontally and vertically oriented Tumbling E's. Another stimulus commonly used in the measurement of VA is the Landolt C. Two studies have been carried out to investigate the differences between horizontal and vertical Landolt C's, with contradictory results. Pascal and Abadi (1995) found those with idiopathic nystagmus (6 subjects) had a "slightly" better VA when the gap of the Landolt C was placed horizontally (0.45 LogMAR) compared to a vertical gap position (0.49 LogMAR). However, the authors did not present a statistical analysis to support this suggestion. In contrast, those subjects with nystagmus associated with albinism showed no difference between horizontal and vertical gap position (6 Subjects). However, no VA data for horizontal or vertical acuity was given. Pascal and Abadi used three different types of stimulus; Landolt C without bars, and Landolt C with distant, and with close bars to create a crowding effect (contour interaction). The VA values for the different orientations for the idiopathic group were taken as a mean across all types of stimuli used (with and without contour interaction). Yet again, no statistical analysis was reported. Conversely, Chung and Bedell (1995) found no difference between horizontal (mean 0.11 ± 0.35) and vertical (mean 0.10 ± 0.32) gap position with their 4 subjects who had idiopathic nystagmus. These data were presented as a table of individual values for each subject and, as with Pascal and Abadi, no statistical analysis was carried out. This lack of statistical evidence means that no definitive conclusions can be drawn as to the effects of optotype stimulus orientation on the VA of people with nystagmus.

Although Tumbling E's, Landolt C's and gratings can all be used to measure VA, the previous paragraphs have shown that, with the exception of gratings, we are as yet unaware of any limitations in the vision of people with nystagmus linked to stimulus orientation. The Tumbling E can be likened to a grating (Figure 4.1A), i.e. the limbs of the letter being like the

bars of the grating, the combination of light and dark bars giving the Tumbling E 2.5 “cycles” in terms of spatial frequency. However, it is less clear how Landolt C’s relate to gratings. It is proposed here that a horizontal Landolt C is the equivalent of a horizontal grating with a spatial frequency of 1.5 cycles. This is better shown diagrammatically (Figure 4.1B), the white bar of the grating being more alike in size to the width of the centre of the Landolt C than to the gap.

Figure 4.1: Stimulus and equivalent gratings for (A) Tumbling E, and (B) Landolt C

The aims of this investigation were to:

1. Discover any underlying horizontal / vertical anisotropy present when using Landolt C, Tumbling E and grating stimuli.

2. Determine whether the VA measured with these stimuli are comparable.

More formally, we sought to test the following hypotheses:

- As with gratings, there will be a better VA found for Landolt C’s and Tumbling E’s when positioned with gaps / limbs horizontally.

- There is no significant difference between the acuities measured with the Tumbling E and Landolt C.

4.2 Methods

Twenty-one subjects with INS and twenty control subjects were recruited, as described in section 3.1. Clinical information regarding the subjects used in this investigation can be found in Appendix I (nystagmus) and Appendix II (controls). No additional prior exclusion criteria were adopted for this investigation. Subjects first had their clinical VA measured using a LogMAR chart calibrated for 4m. Each letter was scored individually, and threshold was taken as the score at which 4 errors were made on a line of 5 letters.

VA was measured by subjects performing a 2AFC staircase procedure as described in section 3.2. Three visual stimuli were used: Landolt C's, Tumbling E's and gratings. For the optotypes, the task was to identify the orientation of the stimulus (up or down for the vertical tasks, and left or right for the horizontal). For the gratings, the vertical gratings were positioned with an angle of ±10° from vertical, and horizontal gratings were positioned with an angle of ±10° above or below horizontal. The task for the gratings was, in the case of the vertical orientation, to identify the grating as "slanting" to the left or right of horizontal (Figure 4.2a); in the case of horizontal gratings, the task was to identify the grating as sloping down to the left or down to the right (Figure 4.2b).

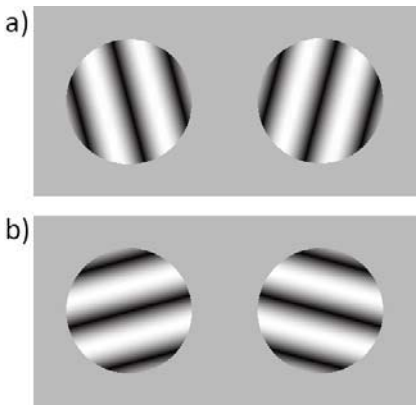

Figure 4.2: Diagram of the grating stimuli presented to the subjects for a) vertical orientation, and b) horizontal orientation

Subjects viewed a sine wave grating through a circular aperture (Figure 4.2). The white luminance was 85.10cd/m², the black luminance was 0.01cd/m² and the mid-grey (background) luminance was 38.40cd/m². The Michelson contrast value was calculated to be 0.9998. In order to keep the visual task as similar as possible for all stimuli, the number of cycles (one cycle being one dark and one light bar of a grating) was set to 2.5, i.e. similar to the limbs of a letter E. The stimuli were presented at the centre of a 21" Sony CRT monitor at 3m. Separate staircases were performed for each stimulus and orientation. The step size was set at 10% of the size of the previous stimulus. The staircase was terminated after 80 presentations. Each stimulus was presented for 1s with a 1s waiting time for the subjects' response. A correct response within these 2s resulted in a beeping sound. No response or an incorrect response resulted in a noticeably lower pitched beeping sound. The duration of each staircase was approximately 160s. No eye tracking was used during this investigation. The head was unrestrained, and INS subjects were allowed to use their preferred null position. All subjects wore their habitual optical correction.

The grating stimuli were calibrated by entering spatial frequencies (SF) from 0.25 to 7 and measuring the width of each bar. Each bar width was then used to calculate LogMAR VA, which was then plotted against inputted SF. The equation of the best fit line between LogMAR VA and SF was derived using Microsoft Excel, and then used to convert the output values into LogMAR thresholds for each staircase. For the Landolt C and Tumbling E stimuli, the inputted values related to the width of the gap (Landolt C) and bar (Tumbling E) in pixels. Again, the size of the gap or bar was measured and used to calculate LogMAR VA. The LogMAR VA values were then plotted against the input (i.e. width of gap or bar) values and

the equation of the line derived using Microsoft Excel. This equation was then used to calculate LogMAR VA from the outputted thresholds for each staircase.

4.3 Results

The age range of subjects with INS was between 20 and 71 (mean = 46.0, SD ± 16.2). Seventeen had idiopathic nystagmus, three had ocular albinism, and one had albinism. Twelve male and nine female subjects (n = 21) participated. The age range of control subjects was between 21 and 62 (mean = 36 ± 14.8). Fourteen female and six male control subjects (n = 20) participated. No control subject had underlying ocular pathology.

The raw data showing the VA measurements for each individual subject for all stimuli and orientations can be found in Appendix IV. The following sections will address the main aims of this study separately. All data for this investigation were normally distributed, and so parametric statistical tests were used.

4.3.1 Horizontal / vertical anisotropy

Table 4.1 shows the mean values of VA for the horizontal and vertical orientations of each stimulus for subjects with nystagmus and control subjects. As expected, subjects with nystagmus demonstrated a significantly better VA for horizontally oriented gratings. However, both the Landolt C's and Tumbling E's show no significant difference in acuity between horizontal and vertical. LogMAR has been used as a measure of VA in numerous publications, as well as the employment of comparing and reporting the differences between two VA measurements (Brown and Yap 1995; Little et al. 2007; Christoff et al. 2011).

For control subjects, visual acuity for both the Landolt C and grating showed no significant difference between horizontal and vertical orientations. Interestingly, however, control subjects demonstrated a significantly poorer VA for vertically orientated Tumbling E's.

Stimuli	Mean H VA (LogMAR)	Mean V VA (LogMAR)	Difference (V - H)	P value (Paired T-test V vs H)
Nystagmus				
Gratings	0.47 (SD 0.20)	0.51 (SD 0.22)	0.04 (SD 0.08)	0.023
Tumbling E	0.28 (SD 0.27)	0.27 (SD 0.26)	-0.01 (SD 0.11)	0.683
Landolt C	0.24 (SD 0.29)	0.28 (SD 0.28)	0.04 (SD 0.11)	0.115
Controls				
Gratings	0.06 (SD 0.10)	0.06 (SD 0.09)	0.00 (SD 0.06)	0.747
Tumbling E	-0.22 (SD 0.10)	-0.15 (SD 0.10)	0.07 (SD 0.05)	< 0.001
Landolt C	-0.26 (SD 0.12)	-0.24 (SD 0.10)	0.02 (SD 0.06)	0.218

Table 4.1: Mean values and standard deviations for each stimuli and orientation, *p* values for paired samples t-test comparing orientation. H - Horizontal, V - Vertical

As discussed in section 2.6.1., the VA of people with nystagmus is highly variable (as are other features of nystagmus) and can range from -0.3 to 2.0 LogMAR (idiopathic and those with albinism/ocular albinism) (Abadi and Bjerre 2002). Because of this, it is difficult to present the effects of stimulus orientation graphically by using mean VA. The data were therefore normalised by taking the difference between horizontal and vertical orientations (vertical VA – horizontal VA for each subject) (Table 4.1). Figure 4.3 shows the mean difference between horizontal and vertical orientations for each stimulus for control subjects and those with nystagmus. Positive values indicate a poorer VA vertically; negative values indicate a poorer VA horizontally. Bars represent mean and 95% confidence intervals.

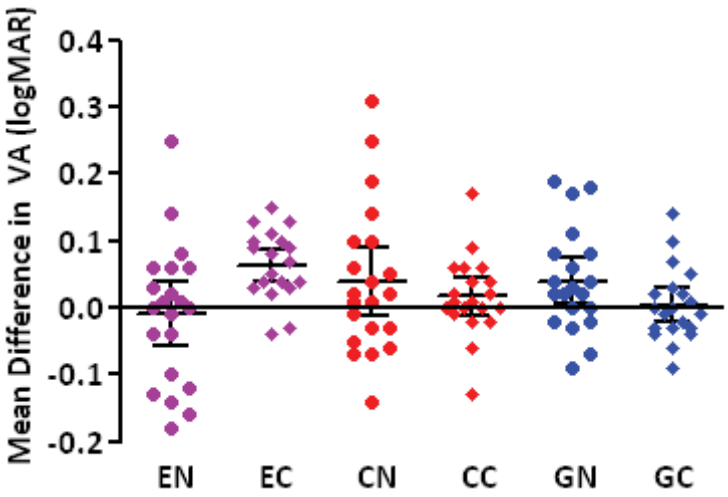

Figure 4.3: Mean difference in VA (LogMAR) between horizontally and vertically orientated stimuli for control subjects and those with nystagmus. Positive values indicate poorer VA vertically. EN - Tumbling E Nystagmus, EC - Tumbling E Controls, CN - Landolt C Nystagmus, CC - Landolt C Controls, GN - Gratings Nystagmus, GC - Gratings Controls

It can be seen from Table 4.1 and Figure 4.3 that, although there is no significant difference between horizontal and vertical orientations with the Landolt C, the mean difference is similar to that found with the gratings for subjects with nystagmus. The lack of significance with the Landolt C may be due to the larger standard deviation with this target and the modest sample size.

4.3.2 Comparison of stimuli

For the comparison of the stimuli used, the mean of the horizontal and vertical VA's was taken. The combined mean of the horizontal and vertical VA thresholds were used in order to remove any bias that may have been present because of the horizontal/vertical anisotropy found with the gratings but not present with the Landolt C and Tumbling E. For example, had we used the horizontal orientations, we would have found a different answer than if we had used the vertical orientation. Taking the average of the horizontal and vertical therefore allowed us to compare just the differences between the three types of

stimuli. Another possible approach might have been to address both the horizontal and vertical orientations individually across stimulus type.

The stimuli were compared using a one way ANOVA with Bonferoni multiple comparison test. VA measured using the grating was significantly poorer than that measured using the Tumbling E or Landolt C. When comparing the Landolt C (mean 0.26 ± 0.28) and Tumbling E (mean 0.27 ± 0.26) to the gratings (mean 0.49 ± 0.21) for subjects with nystagmus, a significant difference was found (respectively CI -0.42 to -0.05, $p < 0.01$ and CI -0.41 to -0.03, $p < 0.05$). Control subjects also showed a poorer VA when measured with the gratings (mean 0.06 ± 0.09), which was significantly different from the Landolt C (mean -0.25 ± 0.11) and Tumbling E (mean -0.19 ± 0.10) (CI -0.39 to -0.23, $p < 0.001$; CI -0.32 to -0.17, $p < 0.001$ respectively). Figure 4.4 shows the mean VA for each stimulus combining both horizontal and vertical orientations for control subjects and subjects with nystagmus. The mean VA's for the Landolt C and Tumbling E were not significantly different for those with nystagmus (CI -0.18 to 0.20, $p > 0.05$). This was also true for control subjects (CI -0.01 to 0.14, $p > 0.05$).

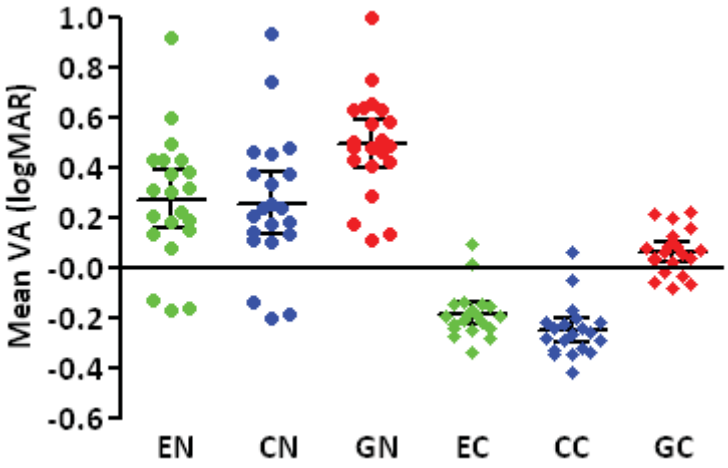

Figure 4.4: Mean VA (horizontal and vertical) for each stimulus for control subjects and those with nystagmus. Positive values indicate poorer VA. EN - Tumbling E Nystagmus, CN - Landolt C Nystagmus, GN - Gratings Nystagmus, EC - Tumbling E Controls, CC - Landolt C Controls, GC - Gratings Controls

4.4 Discussion

These results indicate that, in agreement with previous studies (Abadi and Sandikcioglu 1975; Loshin and Browning 1983; Bedell and Loshin 1991; Meiusi et al. 1993), subjects with nystagmus have a poorer VA when recorded using vertical gratings compared to horizontal. It has long been accepted that VA is worse when gratings are placed at 90° to the maximum nystagmus movements (i.e. as the main movement of nystagmus eye movements is horizontal, the grating would be vertical) (Abadi and Sandikcioglu 1975). This is reiterated by Loshin and Browning (1983), who produced similar findings and again based their conclusions on the predominantly horizontal movements of the eyes resulting in lower sensitivity to high spatial frequencies in the vertical meridian. Bedell and Loshin (1991) indicated that a majority of their subjects had astigmatic refractive error with the negative cylinder axis at or around 180° (with the rule astigmatism). This higher prevalence of astigmatism could also be a causative factor for a meridional amblyopia (if left uncorrected in early years) and hence produce a lower sensitivity to gratings positioned in the vertical meridian. The main question we wished to address in this investigation, however, is how this relates to VA measured using optotypes.

To our knowledge, this is the largest study of the comparisons between horizontal and vertically orientated Landolt C's and Tumbling E's in subjects with nystagmus, and the first to report statistical evidence. The results for the Landolt C indicate no statistically significant difference between VA for horizontal and vertical orientations, which is in agreement with the suggestions of Chung and Bedell (1995), but in contradiction to those made by Pascal and Abadi (1995). We have also shown that there is no significant difference between the VA measured with horizontally and vertically orientated Tumbling E's in subjects with INS.

Control subjects demonstrated no significant differences between horizontal and vertical orientations for both the gratings and Landolt C's. However, a significant difference was found between the different orientations for the Tumbling E, with a poorer VA for vertical stimuli. This has been shown for both Landolt C and Tumbling E stimuli previously (Reich and Ekabutr 2002) in a study which reported the percentage of correct responses to a psychophysical test using both stimuli in both horizontal and vertical orientations. The vertical orientation resulted in a lower percentage of correct response. However, threshold VA was not reported (Reich and Ekabutr 2002). Although Reich and Ekabutr performed an "over refraction" on their subjects' habitual prescription, only spherical alterations were checked for. In the study reported here, retinoscopy was performed to check for any differences from habitual prescription in astigmatic as well as spherical corrections. Habitual prescription was worn as long as it was within ± 0.5 dioptres of the retinoscopy result (both astigmatic and spherical), if outside of this the retinoscopy result was worn (see section 3.0). The two subjects who demonstrated the largest difference between horizontal and vertical orientations had under/un-corrected astigmatism of 0.25DC. However, one subject had against the rule and the other with the rule astigmatism suggesting that the differences are not a result of astigmatic error. Unlike Reich and Ekabutr, we did not find an orientation difference with the Landolt C stimulus. This brings into question the type of task the Tumbling E presents, i.e. if we find a poorer VA for vertical Tumbling Es compared to horizontal, why do we not see this effect in subjects with nystagmus. More research needs to be carried out into this area. As we are primarily interested in subjects with nystagmus, a more in depth discussion is beyond the scope of this thesis.

Both control subjects and those with nystagmus demonstrated a better VA with both Landolt C's and Tumbling E's when compared to gratings. The gratings used in this investigation were high-pass filtered and hence created a "vanishing" stimulus. However, as we were attempting to identify horizontal / vertical differences using standard optotypes, the Tumbling E and Landolt C were not high pass filtered. It is therefore possible that the differences we found between the VA measured with gratings and that measured with optotypes, are a result of the differences between detection and resolution acuity. Detection is the ability to say that a target is present, and resolution is the ability to recognise what the target is. The target size needs to be around five times larger for resolution than for detection, and so two different thresholds are found (Howland et al. 1978). Howland et al. (1978) proposed the use of high pass filtering in the construction of optotypes for VA testing. This consists of a letter, e.g. a Tumbling E, which is constructed of a white letter surrounded by a black line. This is then placed onto a grey background. By adjusting the thickness of the black surround, the luminance of the letter can be matched to the background. Anderson and Ennis (1999) showed that high pass filtering gives similar thresholds for detection and resolution at the fovea using a Tumbling E. The construction of the letters used in the study we report here means that, at close to threshold, the limb side of a Tumbling E appears lighter than the side with the connecting bar. Similarly, the side of the Landolt C with the gap will also appear lighter. It is therefore possible that subjects identified the positioning of the stimulus by these mechanisms and so demonstrated a better VA. The differences we demonstrate in this study are in the order of 0.3 LogMAR and are therefore smaller than the differences suggested by Howland et al. (1978). This could be explained by the nature of the task we presented, which required some degree of resolution (possibly identifying the lighter side of the stimulus), and so the task never became entirely

one of detection. Because of the differences described here, we are limited in the comparisons of VA that we can make between the different stimuli. However, the main interest in this investigation is the intra-stimulus differences of the horizontal and vertical orientations.

There are a number of possible limitations inherent to this investigation. Although VA was measured at 3m, it might have been better to present the stimuli at 6m or greater. Employing eye tracking would also have allowed an analysis of how VA alone might correlate with eye movements in the absence of a stressor. With the current measure of VA, we are unsure of the repeatability of our thresholds. A more ideal procedure would have been for the subjects to attend the unit on a separate occasion and perform the task prior to the orientation experiment so that the two VA thresholds could be compared. However, we were restricted by subject availability i.e. many subjects were only able to attend once. Although the first orientation of each of the stimuli was repeated in order to remove any learning effect, the complexity of the responses needed for the grating task may have been better addressed by repeating both the horizontal and vertical orientations. This could also be true for the Landolt C and Tumbling E stimuli, which might have been addressed by making the tasks a 4AFC procedure rather than two 2AFC staircases. However, this would then make it difficult to separate the VA measured for horizontal and vertical stimuli.

We can safely conclude that subjects with nystagmus demonstrated horizontal/vertical anisotropy to gratings. However, this was not demonstrated for Landolt C's or Tumbling E's. To try to compare acuity between the Landolt C, Tumbling E and grating stimuli used here would be inappropriate, although this could be investigated further using high pass filtered

optotypes. However, in the context of this thesis, our main interest is in the use of standard optotype stimuli to measure VA. Landolt C's and Tumbling E's are therefore stimuli that can be used for VA testing in subjects with nystagmus because neither show any bias based on orientation. However, because of the uncertainty surrounding the Tumbling E with regards to the orientation effects seen in the control subjects, the Landolt C was chosen as the stimulus to be used in subsequent studies**.**

Chapter 5: The Validation of TENS as a Clinical Stressor

5.1 Introduction

When performing investigations that attempt to produce heightened anxiety (arousal), it is essential to be able to measure any change of such states in subjects. As discussed in section 2.7.2, there are a number of physiological changes that occur when subjects are placed under stressful conditions; namely, an increase in heart rate, respiration, increased attention, sweating and/or muscular tension (Motzer and Hertig 2004). Of these changes, the most accessible for measurement are the increases in heart rate and sweating.

5.1.1 Heart Rate

Exposure to a stressor results in increased heart rate due to excitation of the sympathetic nervous system. A discussion of the methods of measuring heart rate is beyond the scope of this thesis, but many studies have previously reported the effects of stressful situations on heart rate (Malmstrom et al. 1965; Taylor and Epstein 1967; Noteboom et al. 2001). Taylor and Epstein note that the variation in heart rate was a result of "rebound" to a previous reaction. For example, a rise in heart rate is followed by a reduction. They conclude that, as the heart plays a role in homeostatic control, and is therefore influenced by other factors other than arousal, it is a poor measure of general arousal (Taylor and Epstein 1967). Malmstrom et al. (1965) found no correlation between the stressful content of a film (previously shown to cause increases in autonomic arousal) and heart rate. They suggested a new method of analysis (mean cyclic maxima) which provided better correlation, although no statistical test was found to be entirely sufficient and so statistical analysis was hindered.

For this method, the values of the peaks of each cyclic increase in heart rate were averaged over a period of time, thus giving a mean maximum heart rate for that time period (Malmstrom et al. 1965).

5.1.2 Skin Conductance (SkC)

Skin conductance (SkC) is a measure of electrodermal activity. Measurement of electrodermal activity had been reported as early as 1879, but many of the modern techniques used today began in the 1970's (Dawson et al. 2000).

The measurement of SkC is based on the fact that, as people become aroused, sweat rises up the eccrine sweat glands (Dawson et al. 2000; Stern et al. 2001). The sweat then acts as a variable resistor. The higher the sweat rises, the lower the skin resistance and therefore the higher the SkC (note that the sweat does not always overflow onto the skin) (Stern et al. 2001). The units used to measure SkC are microsiemens (µMho). We can thereby use skin conductance as a direct, relatively quantitative measure of a person's level of arousal.

As described earlier, heart rate is a poor measure of psychological stress because it is influenced by other factors (homeostasis). In contrast SkC is directly linked to psychological/emotional arousal by the sympathetic nervous system. Malmstrom et al. (1965) have also shown SkC to have a good correlation to the known stressful content of a film. Because of the direct and fast links to psychological stress, the chosen method of measuring arousal for this and subsequent investigations reported here is SkC.

5.1.3 Stressor

When we aim to find a stressor to use in vision research, there are a number of factors that we must address. Firstly, as we are measuring eye movements and recording vision, we

must be able to keep the subject's voluntary eye movements to a minimum. For example it would be inappropriate to use the International Affective Picture System (IAPS). The system comprises a set of colour photographs, which elicit certain emotional responses (Lang et al. 1997; Mikels et al. 2005), and increase arousal (Mardaga et al. 2006). Naturally subjects will scan the picture, which will disrupt fixation. Secondly, we require a stressor that can provide a prolonged level of stress/anxiety to allow us sufficient time to use standard methods to measure VA.

To deal with these points, a number of ideas were considered but abandoned because of the possibility of the subject losing fixation. For example, one proposal was to ask subjects to carry out mental arithmetic whilst performing the acuity test. However, observations suggest that often people will look away when thinking. This may cause difficulty in the measurement of nystagmus eye movements, as these vary with eye position. A case has also been noted of a father and daughter whose nystagmus ceased when carrying out mental arithmetic (Reinecke 1997). This suggests that this is not an appropriate stressor for all subjects.

Yang et al. (2005) investigated the effects of time restricted visual acuity measures on subjects with nystagmus. They concluded that, compared to non-time restricted VA measures, INS subjects showed a decrease in their VA. It could be argued that having a time restriction on the task being carried out simulated a "task demand" or a stressor. However, no eye movement or SkC recordings were made during their investigation in order to ascertain whether there were any changes to the nystagmus waveforms or changes in arousal.

The threat of an electric shock has been shown to increase both SkC and heart rate (Spielberger 1975; Chua et al. 1999; Gray et al. 2003), this change in response to a mere threat has been termed “Anticipatory Anxiety”(Chua et al. 1999). The evidence indicates that this type of stressor can heighten arousal (stress) for a long enough period to measure VA using traditional techniques. A safe and convenient way of administering small electric shocks is by trans-cutaneous electrical nerve stimulation.

Trans-cutaneous electrical nerve stimulation (TENS) has been well documented as a source of pain relief for many years (Karell 1976; Hansson and Ekblom 1983; Willer 1988; Jakoubek et al. 1989). These devices are commercially available and work by interrupting the nervous signals from the area of pain. It is also known to stimulate the release of certain neurotransmitters such as GABA from the brain and spinal cord (Maeda et al. 2007). A secondary effect of the TENS machine is that it causes mild contraction of the muscles over which the electrodes are placed. At higher levels, this can become irritating for subjects. Although the TENS machines use electrical impulses, it has been shown to have no significant effect on recordings of SkC levels (Golding et al. 1985). Therefore, this indicates that any changes found when recording SkC levels will be a result only of increased anxiety/stress. The study described below used non-nystagmus subjects to determine the validity of using the TENS machine in later studies of the effects of stress on nystagmus.

This investigation aims to validate the use of a Transcutaneous Electronic Nerve Stimulation (TENS) machine as a clinical stressor.

5.2 Methods

5.2.1 Subjects

Twenty subjects (without nystagmus) were recruited as described in section 3.1. The age range of the subjects was from 20 to 60 (Median 27, inter-quartile range: 25 – 32). Twelve male and eight female subjects were used. In accordance with the manufacturers recommendations, subjects were excluded from participating if they might have been pregnant, suffered with leprosy or any skin disease, had chronic alcoholism, had heart conditions or were fitted with a pacemaker (Want 2007).

5.2.2 TENS

The TENS machine used in this study is available from Lloyds Pharmacy and has 8 intensity settings (1 to 8), and 8 mode settings (A to H). The change in the mode relates to increases in the frequency of the bursts from the TENS, “A” being the lowest and “H” the highest. The maximum current of the TENS is 30mA ± 20%, with a maximum voltage of 80V ± 20% (Want 2007). The TENS comprises two self adhesive pads, which are placed on the skin of an arm or leg approximately six inches apart and then connected to the main unit. The TENS machine is shown in figure 5.1.

Figure 5.1: Picture of TENS machine. Taken from http://www.lloydspharmacy.com/wps/portal/products/medicalelectrical/relaxationandpain (2008a)

For the purposes of this investigation, the electrodes of the TENS machine were placed on the fore and upper arms of the right arm (Figure 5.2).

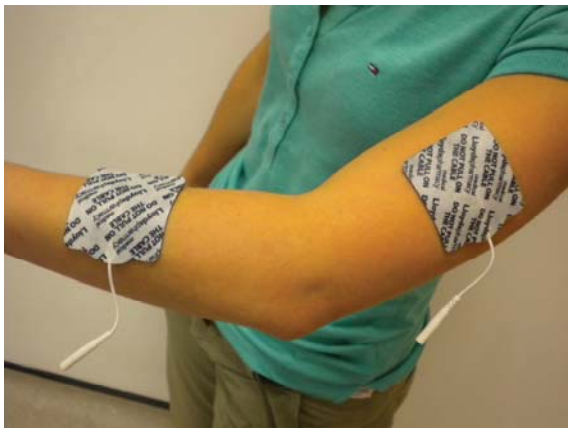

Figure 5.2: Positioning of the TENS pads on the arm of a subject

5.2.3 Skin Conductance (SkC)

Skin conductance was measured using a Biopac MP30 physiological amplifier (Figure 5.3A) and BSL Pro software version 3.6.7 (Linton instruments Ltd, Diss, UK). Readings were taken through a 50Hz low pass filter with gain set at x2000. In order to detect subtle changes in SkC, the sampling rate was set at 200Hz. As subjects were only required to sit as still as possible for this investigation, either hand could be used. For consistency for all subjects, SkC electrodes were placed on the first and middle fingers of the left hand (Figure 5.3B).

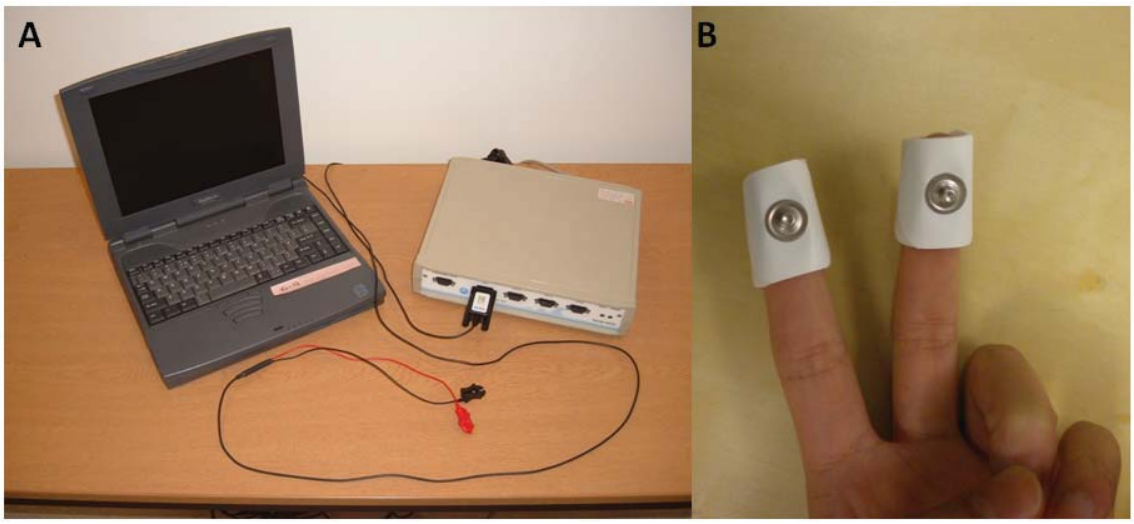

Figure 5.3: A) Biopac MP30 physiological amplifier and Laptop used to measure SkC. B) Positioning of SkC electrodes on first and middle fingers

5.2.4 Protocol

Subjects were seated in a chair and instructed to remain as still and as quiet as possible, as movement may affect the SkC readings. The investigation was split into a series of 5 minute intervals as follows:

- First 5 minute period of relaxation (R1)
- Measurement of TENS threshold (TT)
- Second 5 minute period of relaxation (R2)
- 5 minute period of Anticipatory Anxiety (AA)
- Third 5 minute period of relaxation (R3)

For the measurement of TENS threshold, the TENS machine was set to mode A (the lowest frequency setting) and stepped up by one intensity level at a time (each setting was left on for 20s). At each increase in intensity, a marker was set on the SkC trace. Subjects were told

to say when they did not wish the intensity to be increased any higher (i.e. their threshold for tolerance of the stimulation). The increase in the TENS was terminated when the subjects requested, or when the intensity reached the maximum level of 8. During the AA period, subjects were told that they could receive a burst from the TENS machine at any time, and that the intensity would be **double** that which they experienced during threshold testing. However, this was **never** actually the case. The mode setting was simply changed from A to E (a higher frequency mode). This created a purely psychological stress, i.e. anticipatory anxiety.

5.3 Results

Figure 5.4 shows two typical SkC traces for this investigation. We can see from these traces that SkC increased during TT, showing heightened anxiety/arousal when the threshold for the TENS was being established. SkC then decreased in the subsequent relaxed state (R2) before showing a pronounced increase at the onset of the AA period. In this case, the visible spike at the onset of the AA period indicated that stress/arousal was increased by merely telling subjects what was about to happen. During the AA period subjects received a burst from the TENS machine at random intervals. Following the initial peak, SkC dropped slightly, suggesting habituation to the TENS. However, mean SkC was still maintained at a higher level during this period compared to any of the resting states. SkC traces were analysed by calculating the means for each of the five periods (R1, TT, R2, AA, and R3). This was done by highlighting these areas on the SkC trace and using the computer programme (Biopac BSL Pro 3.6.7) to calculate and display the mean. The raw data for all subjects are shown in table 5.1.

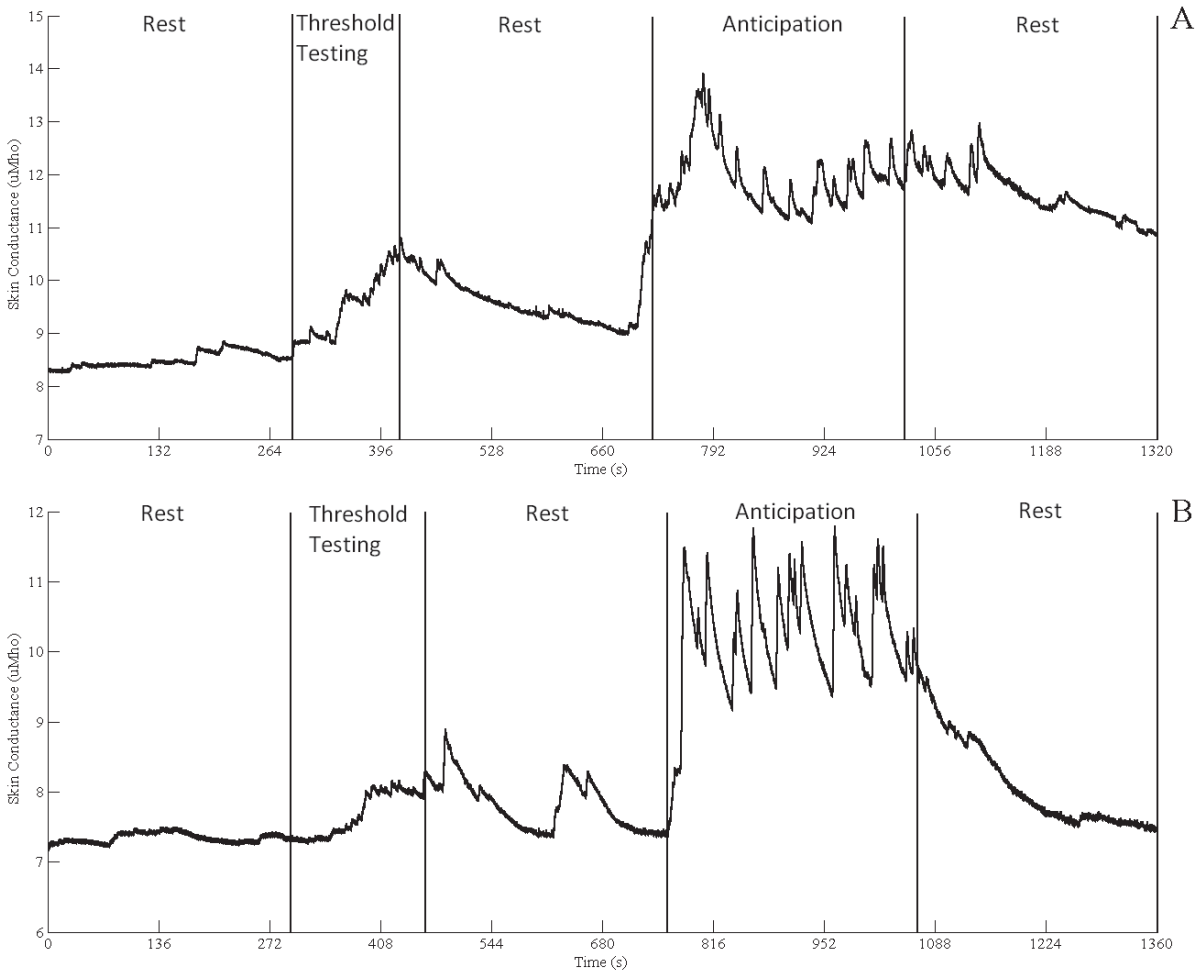

Figure 5.4: Raw data showing two typical SkC traces for subjects GM (A) and SA (B) for the duration of the investigation.

Average resting levels for the SkC are between 2 and 20 µMho (Stern et al. 2001). The generally accepted minimum "significant" change in the amplitude is 0.05µMho, thus indicating an emotional rather than a purely physiological change (Dawson et al. 2000).

Subject ID	Age/Sex	R1	TT	R2	AA	R3
AA	37/M	13.85 (0.29)	14.96 (0.40)	14.83 (0.32)	15.37 (0.76)	16.17 (0.58)
AB	29/M	16.28 (0.13)	17.06 (0.59)	18.55 (0.53)	19.45 (0.20)	19.56 (0.31)
ABi	32/F	7.78 (0.24)	8.65 (0.25)	9.51 (0.28)	11.26 (0.33)	12.01 (0.10)
AM	23/F	13.06 (0.58)	17.74 (1.52)	17.06 (0.61)	17.09 (0.34)	16.31 (0.41)
AW	23/M	11.53 (2.45)	18.23 (1.02)	21.47 (0.77)	23.05 (0.33)	25.88 (2.00)
CP	20/M	21.33 (1.97)	26.63 (1.98)	25.29 (0.62)	26.89 (1.90)	25.27 (1.40)
DM	28/F	8.04 (0.52)	12.40 (3.70)	10.76 (1.50)	9.28 (0.42)	8.40 (0.15)
FG	27/F	8.10 (0.32)	9.15 (0.32)	9.77 (0.16)	10.83 (0.27)	10.60 (0.11)
GF	25/M	15.75 (0.18)	16.37 (0.37)	16.47 (0.27)	16.29 (0.27)	15.78 (0.16)
GM	26/M	8.51 (0.15)	9.50 (0.55)	9.63 (0.46)	11.92 (0.58)	11.66 (0.46)
KE	30/F	8.28 (0.16)	9.48 (0.50)	9.71 (0.18)	10.40 (0.43)	10.31 (0.44)
MA	25/M	19.15 (0.41)	20.06 (0.67)	20.44 (0.23)	21.97 (0.27)	22.74 (0.27)
MC	27/M	22.56 (0.77)	25.76 (2.12)	24.24 (0.74)	27.96 (1.10)	26.08 (0.59)
MD	27/M	8.34 (0.44)	9.53 (0.32)	10.71 (0.36)	12.52 (0.33)	13.19 (0.13)
MW	60/F	14.37 (0.77)	16.77 (0.60)	16.33 (0.49)	16.98 (0.88)	15.59 (0.62)
PH	25/M	14.22 (0.54)	17.38 (1.53)	18.92 (0.62)	19.74 (0.94)	17.47 (0.86)
PM	42/M	9.62 (1.17)	14.85 (1.27)	15.57 (1.26)	17.92 (1.77)	17.32 (0.54)
RN	54/F	7.32 (0.05)	7.52 (0.31)	8.22 (0.19)	8.67 (0.42)	8.11 (0.33)
SA	32/M	7.34 (0.07)	7.67 (0.31)	7.82 (0.36)	10.19 (0.79)	8.17 (0.70)
SH	53/F	11.99 (0.24)	13.07 (1.27)	13.50 (1.14)	16.87 (0.96)	16.64 (0.62)

Table 5.1: Mean SkC for each period. Numbers in brackets are SD. R1 - First relaxed period, TT - Threshold testing period, R2 - Second relaxed period, AA - Anticipatory anxiety period, R3 - Third relaxed period

As can be seen in table 5.1, SkC was highly variable and so comparisons between subjects were difficult. In order to normalise the data, the mean SkC for the entire recording of each

subject was measured and subtracted from the mean of each of the respective periods. Figure 5.5 shows the median SkC of all subjects using normalised data. The grouped results from all subjects were then checked for normality using the Shapiro-Wilk test. All but the R1 period were found to be normally distributed. As not all periods had normally distributed data, non-parametric statistical tests were performed.

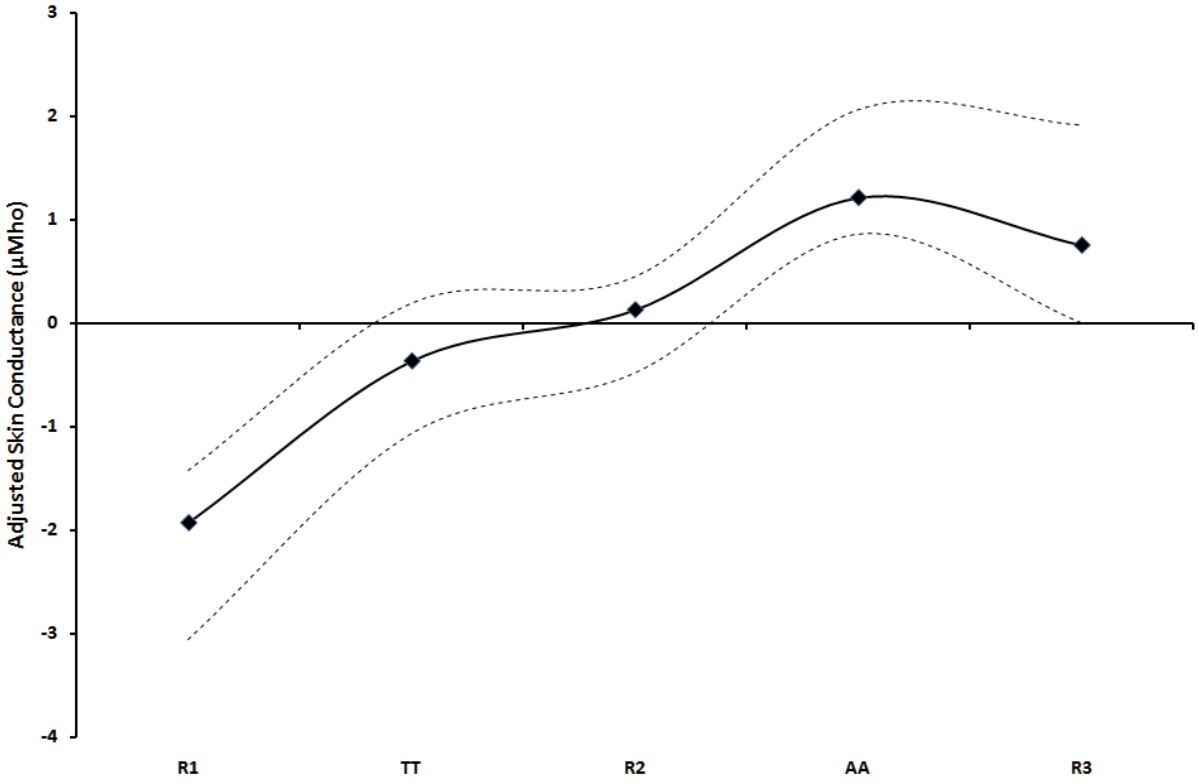

Figure 5.5: Median SkC trace indicating increased arousal during the AA period. Solid line represents median SkC for the duration of the investigation. Dashed lines represent the inter quartile ranges. R1 - First relaxed period, TT - Threshold testing, R2 - Second relaxed period, AA - Anticipatory anxiety period, R3 - Third relaxed period

For statistical analysis, the AA period was compared to the R1 period. All subjects showed an increase in SkC that was greater than the minimum threshold of 0.05µMho (Dawson et al. 2000). This was reflected statistically using the Wilcoxon matched pairs test ($p < 0.0001$). Median SkC for the R1 and AA states are shown in Figure 5.6.

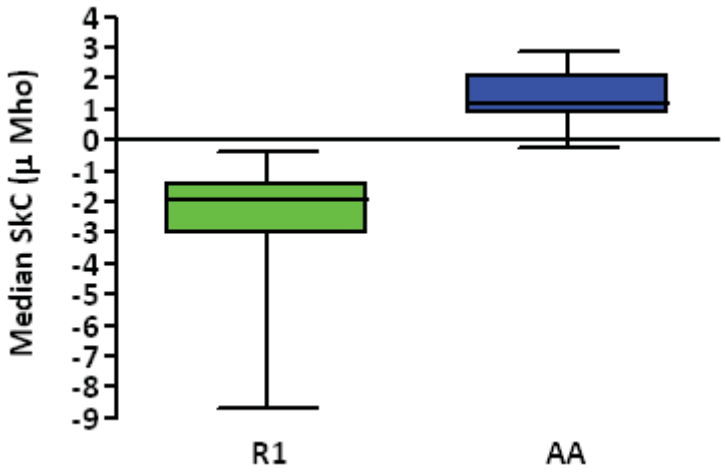

Figure 5.6: Median normalised SkC for the R1 and AA states. R1 - First relaxed period, AA - Anticipatory period

5.4 Discussion

The spread of values for R1 and AA indicate a large variation, confirmed by standard deviations of 5.13µMho and 5.71µMho, respectively. However, all 20 subjects showed a rise in SkC during the AA state. This rise varied between subjects, but all were well above the minimum value of 0.05µMho (Dawson et al. 2000).

The range of resting and anticipatory values found during the course of this investigation indicated that different base levels of skin conductance occur throughout the group of subjects. The amount by which SkC increases is also variable (0.22-3.73µMho). This indicates that, within a population, people will show different emotional responses to a stimulus. Phobias can act as a good example; if a person suffers from a fear of spiders (arachnophobia), then their anxiety will increase if they see a spider. However, for someone who does not suffer with arachnophobia, this change in anxiety will not be seen (Spielberger 1975). In other words, what may be very stressful to one person may not be to another. It is because of this that any investigation aiming to create a state of stress/anxiety can be difficult to control.

The use of the TENS machine (or even its threatened use) provokes an increase in SkC that, even for those subjects with the smallest increase, is above the minimum "significant" value of 0.05µMho used to define an emotional response. Although this minimum value exists, the exact link between SkC and arousal is unclear, i.e. there is no specific grading system that tells us what change in SkC level constitutes mild, moderate or high anxiety.

By using the TENS machine, SkC (and therefore stress/anxiety) was significantly increased for 5 minutes during AA. There was an initial peak followed by a slight reduction; however, SkC was maintained at a higher level, as compared to resting, for the entire 5 minutes of anticipatory anxiety.

The main limitation of this study is that the stressor used was not universally effective for all subjects. As described in the introduction, the TENS machine was the most convenient form of stressor available for several reasons (section 5.1.3). Some of the subjects showed a greater change in SkC than others. However, it is important to point out that a change in the actual level of arousal does not accurately correlate with the absolute level of these differences. Another way of confirming that subjects had become stressed would have been to ask them to complete an anxiety scale questionnaire such as the Spielberger State and Trait Anxiety Inventory (STAI). A second measure of anxiety might also have been useful, i.e. combining heart rate with SkC.

For analysis, the mean SkC of each experimental period was used. However, this does not indicate any changes that may occur within these time periods. It might have been preferable to take several points throughout each period. Another analysis that could have been combined with the t-test to give an indication of any change in the variability (SD) of SkC between each period would be the F-test.

It is concluded that the TENS machine can create a prolonged state of anxiety/arousal and that it can be used in investigations of the effects of stress on the eye movements and visual performance of people with nystagmus.

Chapter 6: The Impact of Stress on Visual Function in Nystagmus

6.1 Introduction

As mentioned in section 2.7.3, until recently there was only anecdotal evidence from those with nystagmus that their vision becomes worse when they are under stress, as well as one observation of a subject whose eye movements "improved" as he relaxed (Abadi and Dickinson 1986). In recent years, attempts have been made to quantify some of the effects of stress on nystagmus. Cham et al. (2008a) investigated the effects of task-related stress on the nystagmus waveforms using 3 different types of task. An "unrestricted viewing" task allowed subjects as long as they required to identify the position of the gap in a Landolt C as being in one of four directions (up, down, left, and right). A "restricted viewing" task which gave subjects only a limited time to identify the gap in the Landolt C. The time limit was adjusted depending on the subject's VA and ranged from 0.2s for those with a VA of -0.1 LogMAR to 2s for those with a VA of 1.2 LogMAR. During the "restricted viewing" task, subjects were also asked to carry out a serial subtraction of 17 from 700 whilst performing the VA task. The third type of task was a "reward manipulation" task in which the subject was informed that, for every 2 correct answers, they would earn $0.50 whereas for every incorrect answer they would lose $1.00. During the "reward manipulation" task, the same time restrictions were also used. Cham et al. used heart rate as their measure of arousal during this investigation. Their results indicated significant increases in amplitude, frequency, and intensity, with a significant decrease in foveation duration from baseline in all the tasks carried out. Despite these changes in eye movement no significant difference in

VA between the three tasks was found. Although these results are of interest, there were a number of methodological limitations. Specifically, the tasks were carried out at 1.6m with subjects keeping their heads in primary position. This means that some subjects were using their null position whilst those with an eccentric null were not. It is known that gaze angle affects nystagmus waveform (i.e. intensity worsens away from the null point) (Abadi and Whittle 1991). The subjects also wore no optical correction, whether they required one or not. By not examining subjects at their null position and failing to provide an optical correction (when needed), eye movement and VA results would not have been representative of "real life" situations for these subjects. Furthermore, they also used a non-standard VA task, i.e. the edges of their stimuli were blurred on purpose in order to increase the levels of stress. Therefore, care must be taken in any conclusions drawn from this study about the effects of stress on VA.

In recent years, some authors have placed greater emphasis on other aspects of "visual performance" in addition to the measurement of static VA when assessing visual capability in those with nystagmus. One such measure is termed "time to see" (Sprunger et al. 1997; Hertle and Reese 2007; Wang and Dell'Osso 2007, 2009a, b). Sprunger et al. (1997) measured "reaction time" to optotypes as an outcome measure following four muscle recessions in the treatment of nystagmus. Hertle and Reese (2007) indicated in their study of contrast sensitivity that "visual reaction time" may be a better measure of visual function in people with nystagmus. The studies by Wang and Dell'Osso (2007, 2009a, b) looked specifically at the time it took subjects to fixate a target (measured from the time the target moved to the first foveation period that is on target). Their study in 2007 used saccadic jumps (moving the stimulus from one fixed position to another) initiated at different times

during the nystagmus cycle. Saccadic latency and the latency of subjects fixating the target (i.e. the time it took subjects to accurately fixate the target) were investigated. The time in the cycle at which the target was moved, the normalised version of this (time in cycle/length of cycle), the original orbital eye position, the initial retinal error, and the final retinal error were all considered as possible factors that may affect the latencies.

Their study reported an increase in the saccadic latency of people with INS and showed that fixation latency was dependent on the time (normalised) in the nystagmus cycle at which the movement of the stimulus occurred (R^2 = 0.54). Fixation latency was also found to be longer when the movement of the stimulus occurred either just before or just after a foveating saccade (Wang and Dell'Osso 2007). This was studied further in 2009 by the use of stimuli moved at 10°/s to the left or the right. Similarly, fixation latency was increased dependent on the time within the nystagmus cycle at which the stimulus was moved (Wang and Dell'Osso 2009b). The conclusion reached in both of these studies is that the measurement of VA by optotype recognition in one position of gaze does not give a true indication of a subject's visual function in the real world. In a review, Wang and Dell'Osso (2009a) recommend, in addition to VA, the assessment of a subject's eye movements in response to moving stimuli in order to better determine visual function in the "real world". As mentioned earlier, this proposal is also supported by previous studies (Sprunger et al. 1997; Hertle and Reese 2007).

In the investigation discussed in this chapter both VA and response time were measured. Response time was a measure of the length of time between the stimulus appearing on the screen and the time at which the subject made a judgement about the position of the gap in a Landolt C, indicating their response using a push button response box.

The aims of this investigation were to:

- Measure the changes in waveform parameters that occur with stress when subjects use their preferred null position
- Measure the changes in VA that occur with stress in both control subjects and those with nystagmus using standard optotypes, at distance, using habitual optical correction and preferred null position
- Measure the changes in response time that occur with stress for both control subjects and those with nystagmus

6.2 Methods

6.2.1 Subjects

Twenty-three subjects with nystagmus (13 female and 10 male) and twenty control subjects (10 female and 10 male) were recruited for this investigation, as outlined in section 3.1. The age range of subjects with nystagmus was 19 to 71 years (mean 44 ± 16.37). The age range of control subjects was 21 to 61 years (mean 34 ± 12.24). Clinical information about these subjects can be found in Appendix I (nystagmus) and Appendix II (controls).

6.2.2 Laboratory Set Up

The laboratory set up for the stress investigation consisted of a two mirror system, shown in figure 6.1a. This configuration allowed subjects to view the visual stimulus at a 7m viewing distance, thus allowing distance VA to be measured without being constrained by the pixel resolution of the display monitor. The two mirror system was made up of a fixed mirror positioned 3.74m in front of a 21” Sony CRT monitor, and a mirror attached to a stepper

motor (controlled by a computer) positioned (centre of rotation) 0.4m in front of the subject (2.86m from the fixed mirror) (Wiggins et al. 2007).

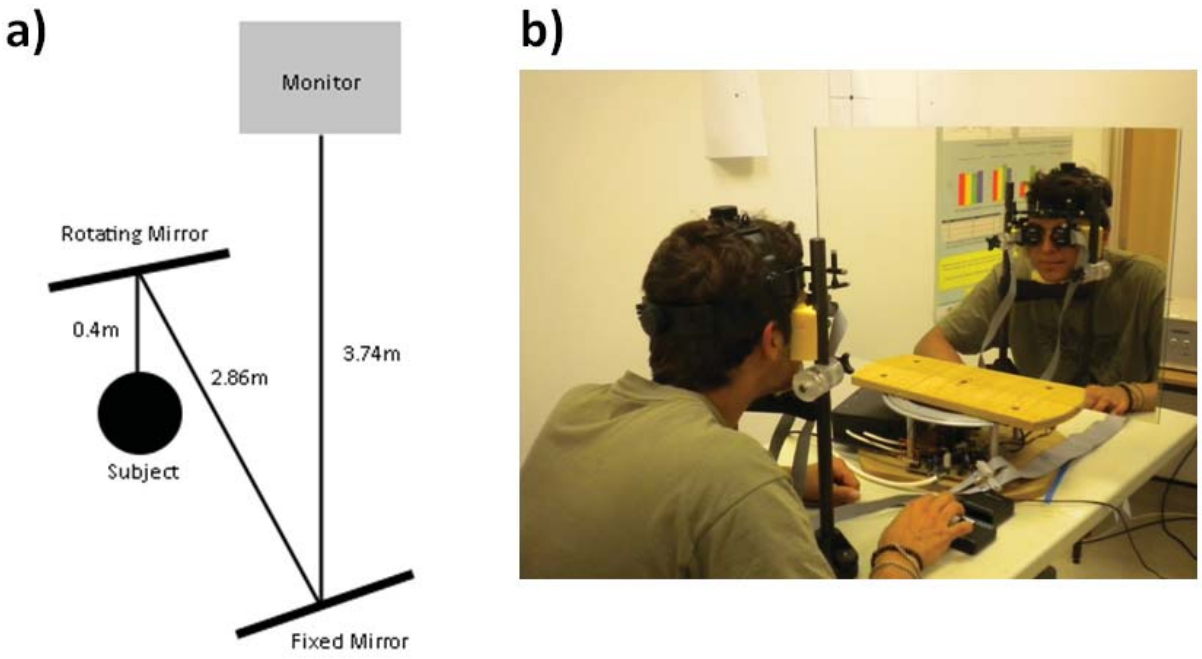

Figure 6.1: (a) Schematic diagram of the laboratory set up (b) subject sitting in front of the motorized mirror

The rotating mirror (Figure 6.1b) was placed on top of a ball bearing turntable attached to a computer controlled stepper motor. In turn, the motor drove a potentiometer which generated a voltage signal which was fed through a National Instruments box (BNC-2110) used to send a position signal to the computer program in a feedback loop. The accuracy of the mirror's position was within ±1°, and the mirror could be moved in order to change the orbital eye position the subject had to use to view the stimulus (i.e. the mirror moved the apparent position of the stimulus) (Wiggins et al. 2007). This is beneficial for subjects with eccentric null positions as the stimulus could then be moved into their null zone, thus normalising nystagmus across subjects because all could use the gaze angle at which their eye movements (intensity) were at a minimum. Null position was determined for each subject by, after calibration of the eye tracker, asking subjects to sit back from the chin rest

and view a target using their preferred head position. The gaze angle was then read off the real time display on the computer programme.

6.2.3 Skin Conductance (SkC) and TENS Machine

Skin Conductance (SkC) was recorded using the Biopac MP30, as described in section 5.1.3, for the entire duration of the investigation (including the periods of time between each of the 4 VA measurements when the computer programme was being reset and the eye tracker calibrated). As a result, the duration of the SkC measures could sometimes exceed 1 hour. In order to reduce the file sizes generated, and because we were only looking for larger changes in SkC between VA measurements rather than subtle changes within each measurement, the sampling rate was set at 50Hz. At the start of the investigation, subjects were asked to wash and dry their hands to remove any natural oils from the skin. The electrodes were then placed on the first and middle fingers of the subject's non-dominant hand (Figure 5.3B), which could be kept still, thereby leaving their dominant hand free to use the push button response box (see later). The TENS machine was used in order to create a feeling of stress, as outlined in chapter 5, with the electrodes placed on the subject's dominant arm (Figure 5.2).

6.2.4 Eye Tracking

Eye tracking was performed during this investigation using the IRIS eye tracker (section 3.2.4). The IRIS system was first calibrated by aligning the eye pieces to centre over each of the pupils and positioning them approximately 1cm away from the eyes. Contact lenses could be worn, but if subjects only had spectacles, their correction was put into a frame attachment in front of the eye pieces of the eye tracker (Figure 3.3) using full aperture trial

lenses. The system was then fine tuned by asking the subject to fixate a target on the wall and adjusting the IRIS eye pieces so that the LED display on the control module was centred for each eye. Subjects then looked between two points on the wall which were positioned so that the eyes moved 20° to the right and left in turn, in order to position the LED display on the control module at its extremes. If each eye piece moved by a different amount on gaze shifting, the gain was adjusted to ensure equal movement. This was done to check that the eye pieces were positioned to give the most accurate recordings. Those subjects with manifest strabismus performed the investigation monocularly.

The most common calibrations used in nystagmus research involve plotting a regression between stimulus location and eye position output from the eye tracker (in the case of IRIS, this is voltage). The stimuli are moved either sinusoidally (smooth pursuit eye movements) (Abadi and Scallan 2000; Clement et al. 2002) or are positioned at several discrete locations (saccadic eye movements) (Simmers et al. 1999; McLean et al. 2007; Cham et al. 2008a). The use of sinusoidal calibration means that a larger number of data points can be plotted (depending on the sampling frequency of the eye tracker used) and so a more accurate calibration can be obtained. This is especially important in people with nystagmus as their eyes cannot usually fixate steadily. In the setup for this investigation, the rotating mirror drove the position of the stimulus; the type of motor used did not allow a true sinusoidal movement and so the system was calibrated by a saw tooth movement with the subject fixating a 0.2° black dot presented on the VDU screen. The saw tooth movement moved the stimulus up to a maximum of ±20° at a frequency of 0.25Hz (by the laws of reflection, the mirror only required a movement of 10° in either direction). Regression analysis was then performed on target position against the voltage output from the IRIS system. In order to

obtain an acceptable calibration, a Pearson's correlation coefficient of >0.85 was required. If this was not achieved, the positions of the eye pieces were rechecked, and calibration was repeated. All eye movement calibrations and recordings were binocular with the exception of subjects with only one fixating eye (i.e. in the presence of a prosthesis or tropia). In these cases, accurate calibration was sought from the fixating eye only.

6.2.5 Visual acuity (VA)

VA was measured by means of a 2AFC staircase procedure as described in section 3.2. For this investigation a Landolt C stimulus with the gap positioned horizontally (i.e. either left or right) was used (see chapter 4). The step size was kept constant at 0.075 LogMAR. Once a minimum of 80 presentations **and** 8 reversals had been met, the staircase continued for 2 more minutes. This allowed optimal time at threshold in order to assess the effects of the stressor on eye movements, VA and response time. Visual stimuli were presented at the centre of a 21" Sony CRT monitor and generated by a VSG 2/3 system (Cambridge Research Systems, Cambridge, UK). The initial stimulus size was set at 0.3 LogMAR above the subject's clinically measured VA. The response to each stimulus was indicated by using a push button response box. Threshold VA was measured by plotting the stimulus size against time for each VA task, and taking the mean of the last 6 reversals. The VA task was performed binocularly for most of the subjects. However, in the case of those subjects with strabismus, the strabismic eye was occluded using a frosted lens in order to prevent subjects from cross fixating or changing fixation during the course of the investigation.

6.2.6 Experimental protocol

Initially, subjects fixated the spot for five minutes. This was done in order to give a sufficiently long fixation recording to allow the identification of PAN (section 2.2.1). The eye movements of subjects who exhibited PAN were excluded from analysis as the quiet and active phases could lead to spurious results. No evidence of PAN was found in any of the patients whose data are reported here.

During this investigation, VA was measured four times. A time line of the experimental protocol is shown in figure 6.2. First, VA was measured under relaxed conditions (R1), this gave the subjects experience of the task and helped reduce any learning effects. Following R1, the subject's threshold to the TENS machine was measured as described in section 5.2.4 by increasing the level by one step every 20s until level 8 was reached or subjects indicated they did not want it to go any higher. The second VA measurement was under "Task Demand" (TD) conditions, in which subjects were told that they would receive a short burst from the TENS machine at **double** their threshold if they gave an **incorrect response** to the visual stimuli. The bursts from the TENS machine were administered by the investigator using a push button. The third VA measurement was obtained during the "Anticipatory Anxiety" (AA) task when subjects were told that they could receive a small burst from the TENS machine at **double** their threshold **at any time**. As stated in chapter 5, the TENS machine was **never** set any higher than the subject's threshold; only the frequency of stimulation was changed.

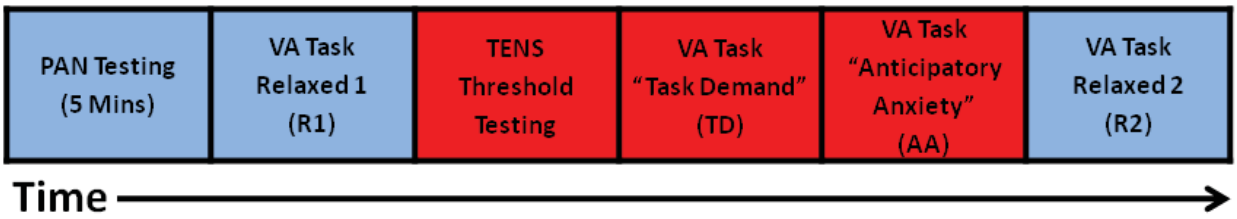

Figure 6.2: Timeline of study. Blue: periods when stressor was not used, Red: periods when stressor was used

6.2.7 Eye movement analysis

As a result of the high sampling rate of the IRIS system (1000Hz), a large amount of data was produced, but only one 6s segment of waveform data from each period (i.e. R1, TD, AA and R2) was chosen for analysis. This duration was chosen as it provides around 24 complete waves (slow drift and corrective saccade) based on an average nystagmus frequency of 4Hz. This approach is similar to other studies on nystagmus which have been carried out by other investigators in the past, in which the length of the waveform analysed ranged from 0.6-40s (Dell'Osso 1973; Kommerell 1986; Abadi and Worfolk 1989; Chung and Bedell 1995; Gottlob 1997; Ukwade et al. 2002; Shery et al. 2006; Cham et al. 2008a). Although this range exists in the literature, the majority of studies have used sampling epochs of 10s or less. Our specific use of 6s epochs also means that we can directly compare our current study with the results of previous investigations by our research group. The utilisation of 6s epochs at threshold also means that our data are not affected by any changes in nystagmus waveform that have been noted with increased visual demand (Wiggins et al. 2007). These 6 second segments of waveform recordings for each period were consistently chosen to be in the middle of the time during which VA was at threshold. The start time was then adjusted so as to analyse the time period with the least number of blinks (Ukwade et al. 2002).

Amplitude, frequency and intensity data were found by analysing, by hand, the waveforms displayed on the screen. Data sets were not masked for analysis. Amplitude data were

obtained by identifying (by hand by the investigator) the beginning and the end of each of the slow phases (Figure 6.3) on eye position recordings displayed on a computer monitor.

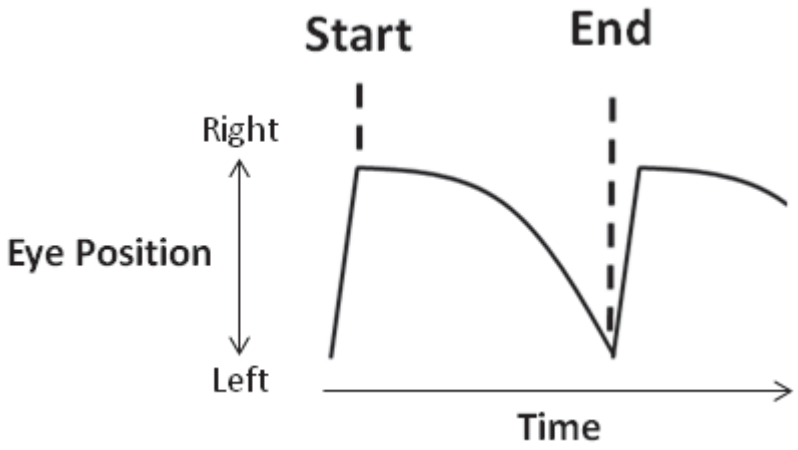

Figure 6.3: Schematic diagram of jerk (J) nystagmus waveform showing the start and end of the slow phase

If the position trace was difficult to interpret, velocity recordings were displayed superimposed on position to aid identification of the saccades (which effectively bracket the slow phases). Analysis by hand was used to remove any computer-based error for the detection of the beginning and end of the slow phases. These data were then exported to a Microsoft Excel spreadsheet. Frequency was determined by the equation below. Intensity was the product of amplitude and frequency.

$$\text{Frequency} = \frac{1}{\text{Time series}}$$

(Time series = the mean duration of the complete phases i.e. slow phase and fast phase during each 6s segment)

Foveation periods were determined using a programme written in MATLAB (version 7.1, The MathWorks, Inc.) by Professor Chris Harris of Plymouth University. The programme first identified all points on the waveform where the velocity was <4°/s. As discussed in section 2.5.1, this velocity criterion has been well established as the threshold for good VA (Burr and Ross 1982; Chung and Bedell 1996). A position criterion was then applied. There has been

much debate about the allowable positional error for foveation (section 2.5.1). For the present study, an allowable error of ±2° was used. This more relaxed position criterion has been used by previous studies (e.g. Dell'Osso and Jacobs 2002; Wiggins et al. 2007). The standard deviation of eye position (SD_P) was also calculated using a programme written by Professor Chris Harris using MATLAB (version 7.1, The MathWorks Inc.). The programme uses the foveations identified by the first programme and calculates the standard deviation of the eye position during these periods.

6.3 Results

6.3.1 Stressful Tasks Increase Arousal

Figure 6.4 shows two typical SkC traces from subjects with nystagmus. A visible increase can be seen during both the TD and AA periods.

As described in chapter 5, SkC recordings were normalised for each subject by subtracting the mean of the entire recording from the SkC recorded during each of the VA tasks. Subjects with nystagmus showed higher SkC readings during both the TD and AA periods. Testing for normality using the Shapiro-Wilk test revealed the data from all but the R1 period to be normally distributed. Therefore, the more conservative non-parametric tests were used. Figure 6.5 shows the median SkC traces for subjects with nystagmus for the entire investigation. The R1 period was performed in order to remove any learning effect from the VA task. The data from the R2 period was therefore compared to the TD and AA periods. Peak arousal was observed during the TD period: median increase (from R2) 1.52µMho, inter-quartile range 0.37 – 2.20µMho (Wilcoxon matched pairs test, $p < 0.001$).

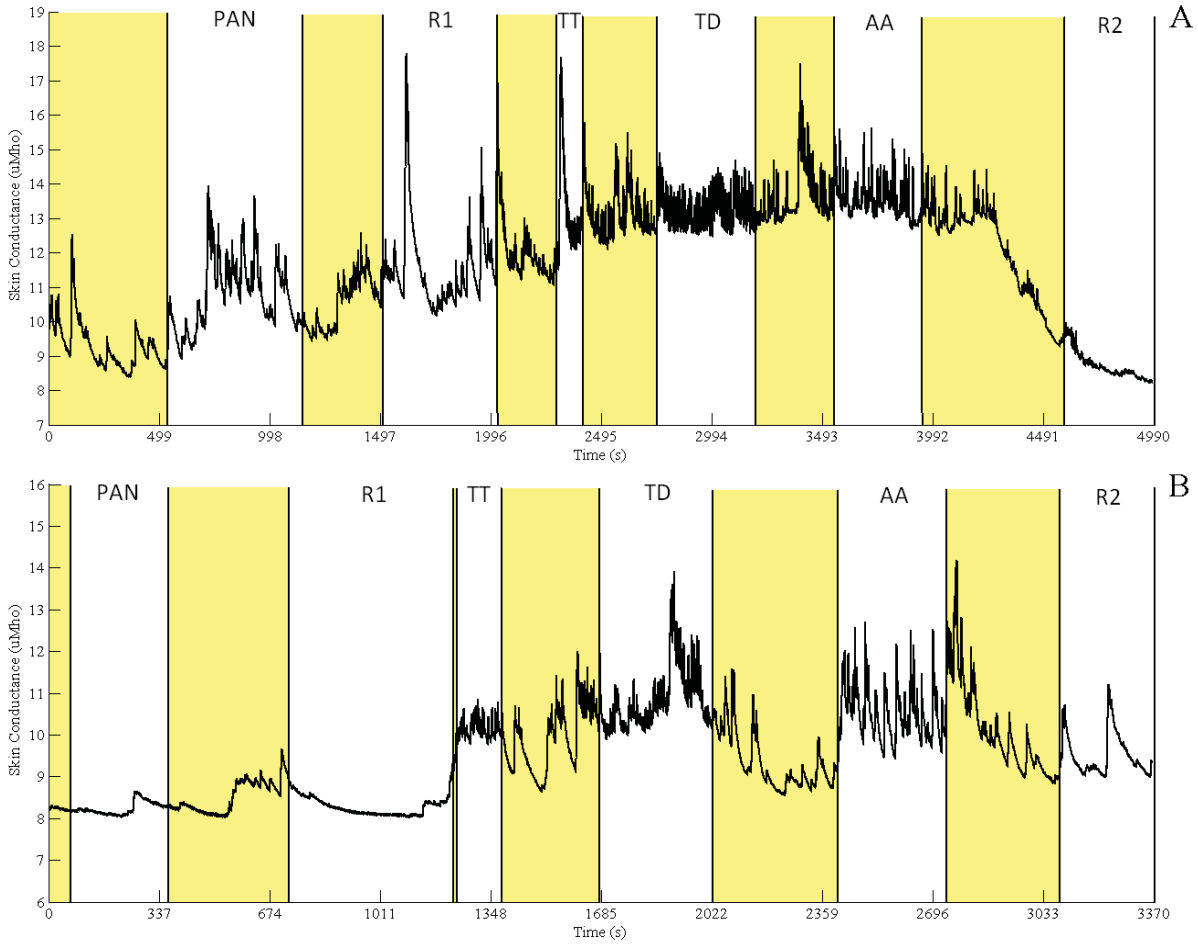

Figure 6.4: SkC traces for two subjects with nystagmus CT (a) and GT (b). Coloured areas indicate periods between VA measurement where the computer programme was being reset and recalibrated

The median increase during the AA period was lower than that in TD (0.45µMho, inter-quartile range -0.05 – 1.22) but still showed a significant increase from R2 (p = 0.016). During TD, SkC was significantly higher than during AA (p = 0.009), indicating that the TD period is the most stressful for people with nystagmus. Control subjects also exhibited a significant increase in SkC during the TD period (p = 0.036) and the AA period (p = 0.026) (Figure 6.6). However, there was no significant difference in SkC between TD and AA for control subjects (p = 0.922). Three of the subjects with INS showed a slight reduction in SkC suggesting that they did not become stressed. However, removal of these subjects from subsequent waveform analysis has no impact on the results that we find.

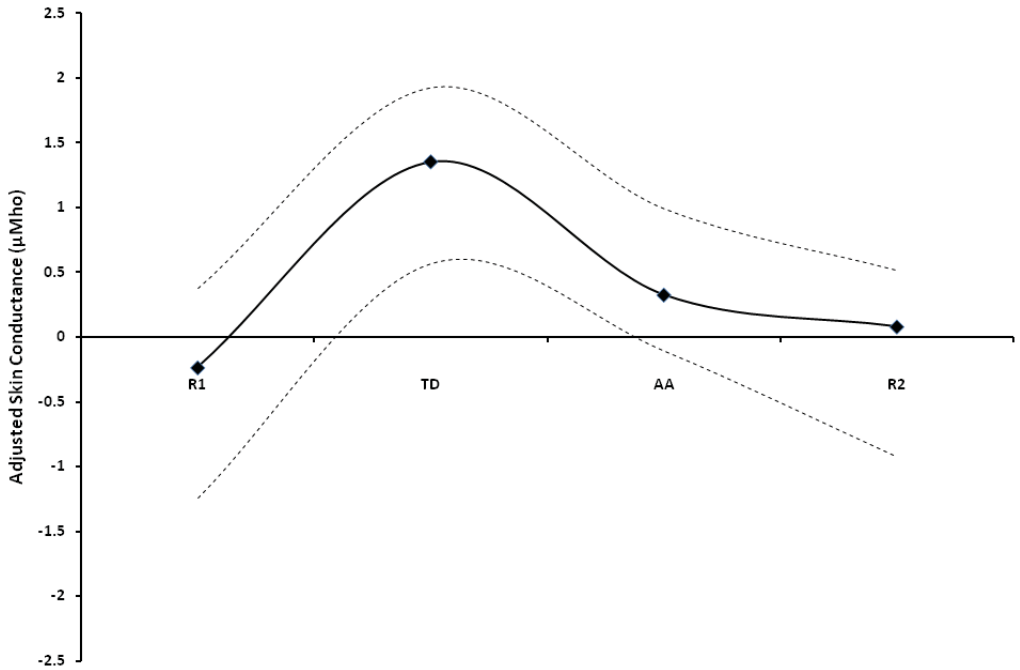

Figure 6.5: Median SkC for subjects with nystagmus for the duration of the study. Solid line: Median SkC, Dashed lines: inter-quartile ranges

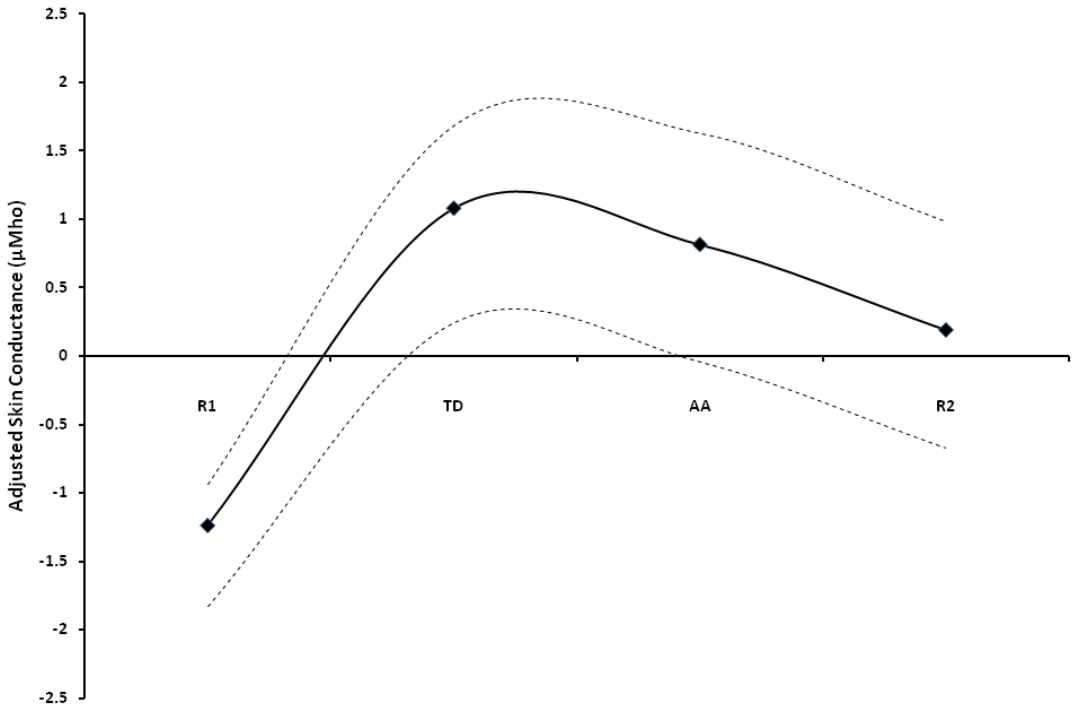

Figure 6.6: Median SkC for control subjects for the duration of the study. Solid line: Median SkC, Dashed lines: inter-quartile ranges

6.3.2 Stressful tasks have a negative effect on nystagmus waveform

As discussed in section 6.3.1 the largest increase in SkC was found during the TD period. Figure 6.7 shows waveform recordings for three subjects during the TD and R2 periods.

The Shapiro-Wilk test for normality indicated that, of the waveform parameters measured, only frequency data were normally distributed in all four of the testing periods. Non-parametric stats (Wilcoxon matched pairs) were therefore applied to all data.

In agreement with Cham et al. (2008a), waveform characteristics changed when subjects were placed under stress (particularly task demand type stress). Figure 6.8 shows the median amplitude, frequency and intensity for the R1, TD, AA and R2 periods.

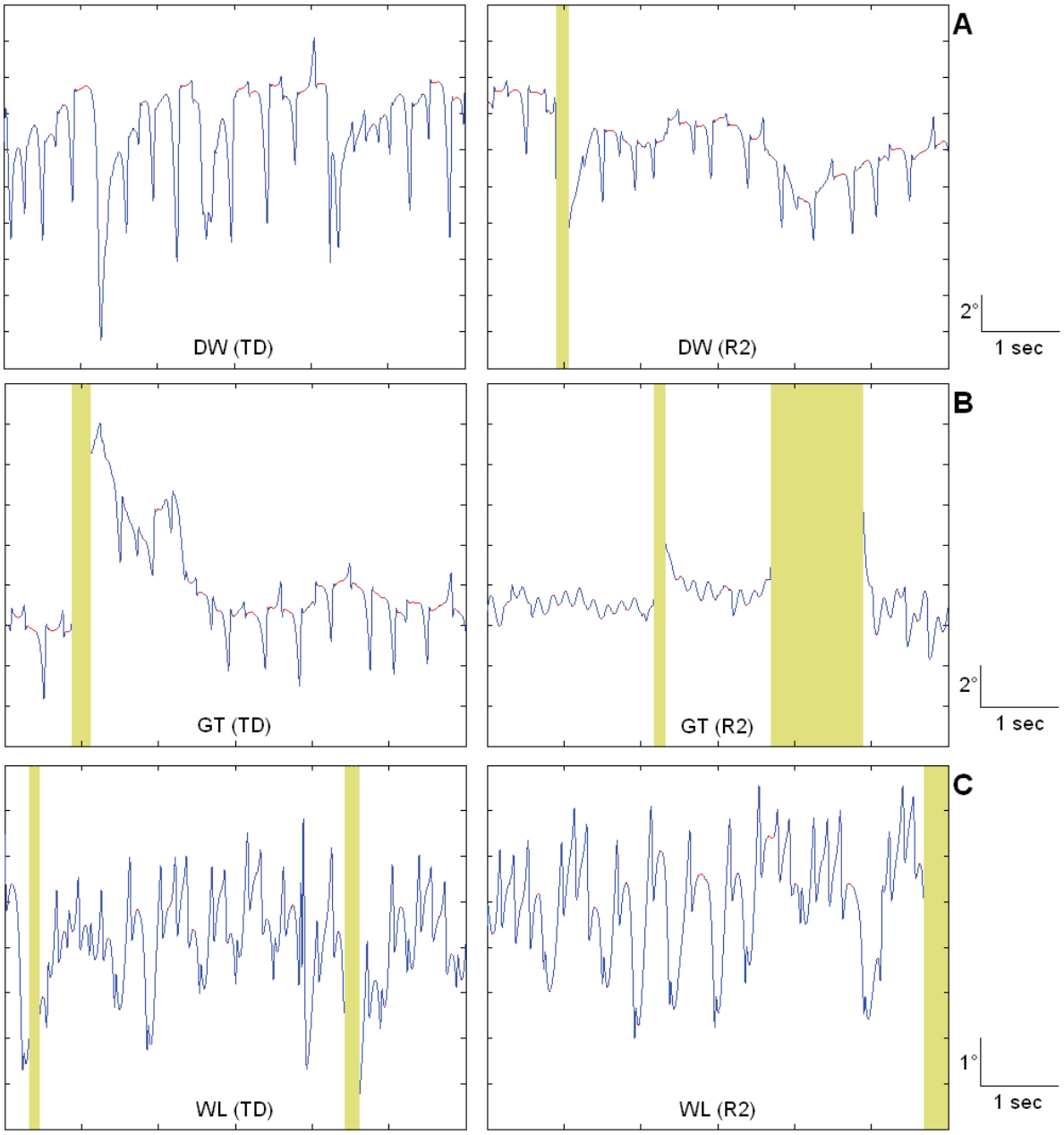

Figure 6.7: Eye movement traces of eye position against time for the "Task Demand" (TD) and "second relaxed period" (R2) periods of three subjects with nystagmus, (A) DW, (B) GT and (C) WL. Individual scales are shown alongside each pair of traces. Fawn blocks indicate blinks

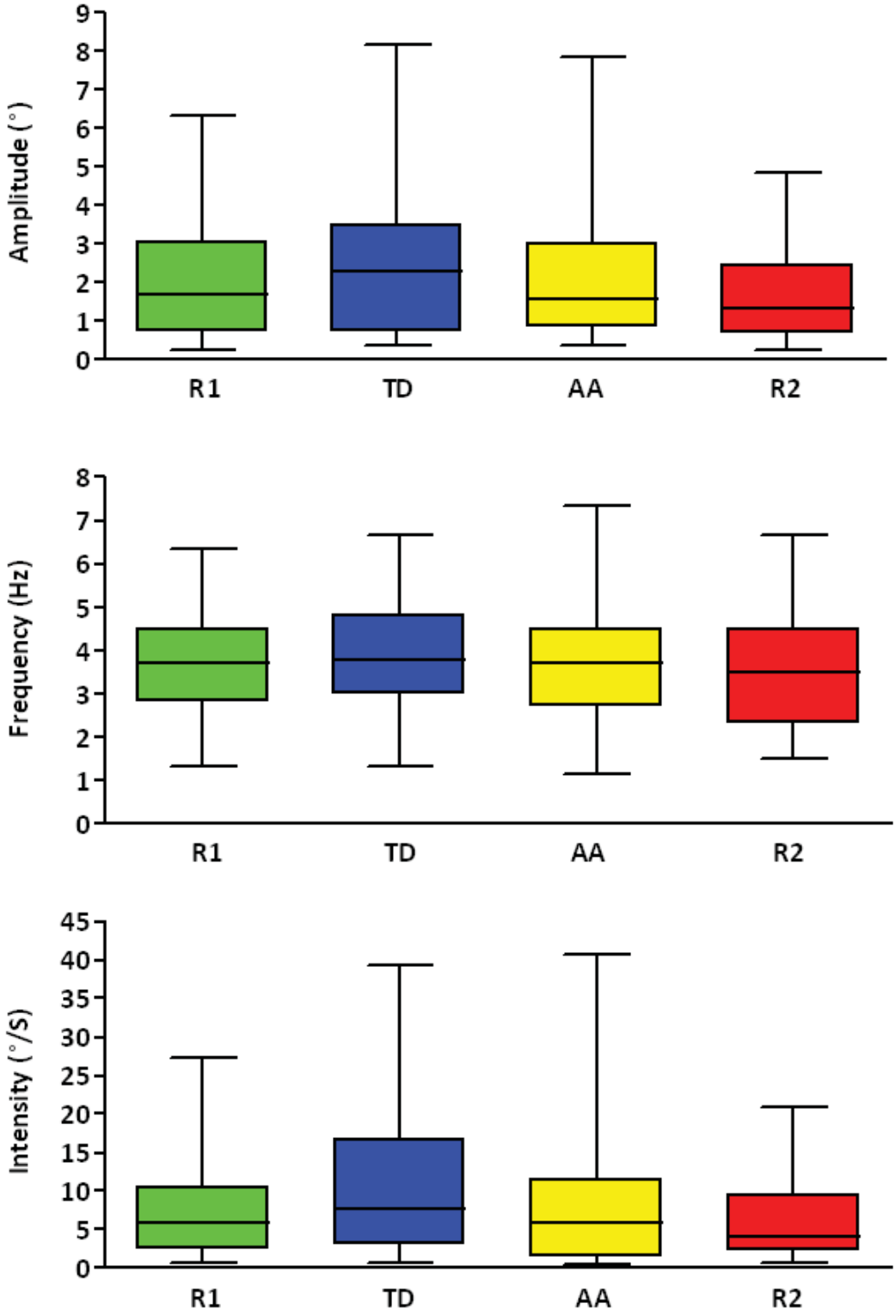

Figure 6.8: Median amplitude, frequency and intensity for 23 subjects with nystagmus. R1 - First relaxed period, TD - "Task Demand" period, AA - "Anticipatory Anxiety" period, R2 - Second relaxed period

When compared to the R2 period, amplitude significantly increased during the TD period; median increase of 0.68° (p = 0.005). Although there was also an increase during the AA period, it did not reach significance (median increase 0.12°, p = 0.079). The frequency of the waveforms did not significantly change during either the TD or AA periods (p = 0.12 and p = 0.35, respectively). However, intensity (amplitude x frequency) significantly increased during the TD period (median increase 1.88°/s, p = 0.003) but again this was not significantly increased during the AA period (median increase 0.87°/s, p = 0.061) (Figure 6.8). It is worth noting that five subjects actually demonstrated a reduction in intensity during the TD period (Table 6.1). However, of these five subjects, only one demonstrated a reduction in SkC during the TD period.

Subject	Intensity R1	Intensity TD	Intensity AA	Intensity R2
CM	26.91	16.75	16.23	14.41
SW	2.07	2.08	1.36	2.83
LC	5.8	3.07	1.36	2.26
RB	27.39	12.2	17.37	9.53
KL	0.63	0.97	1.56	1.18
JqA	6.94	4.83	8.43	8.87
JeSt	17.19	19.55	14.39	12.6
MH	7.9	16.23	5.96	2.22
CT	1.17	3.02	1.82	1.49
DW	16.06	21.01	7.04	9.34
GT	13.99	18.14	4.02	5.58
JS	2.40	39.22	40.73	20.85
LL	5.83	6.84	5.9	3.13
VO	5.49	7.83	7.37	5.95
MB	2.95	0.6	0.59	0.98
MT	2.94	3.34	3.98	2.64
JM	9.34	9.46	5.04	4.17
RC	0.74	2.14	0.93	0.63
RW	10.51	22.46	21.09	12.81
WL	10.55	8.39	11.15	8
VW	9.27	7.71	11.51	19.27
RN	1.87	4.21	4.61	2.99
CW	5.09	5.67	1.46	0.95

Table 6.1: Intensity values for all subjects. The five subjects demonstrating reduced intensity during the TD period are highlighted

The increase in intensity during TD was associated with a reduction in foveation duration. The average foveation duration per complete nystagmus cycle had a median reduction of 20.21 milliseconds (ms) during the TD period (p = 0.016). The average foveation duration per complete nystagmus cycle was not significantly reduced during the AA period; median difference 3.46ms (p = 0.350). This is shown in figure 6.9.

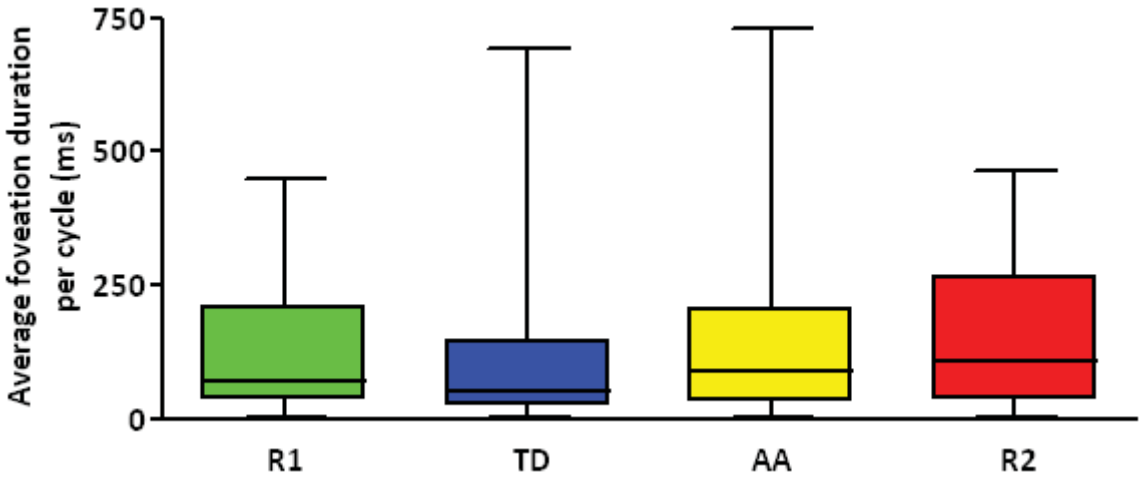

Figure 6.9: Median foveation duration per cycle for all four periods of the study. R1 - First relaxed period, TD - "Task Demand" period, AA - "Anticipatory Anxiety" period, R2 - Second relaxed period

The difference in standard deviation of eye position (SD_p) during the foveation periods were tested using the Friedman analysis of variance test. No significant difference was found between the SD_p of the TD and AA periods when compared to R2 ($p > 0.05$).

Three subjects showed a change in their predominant waveform during the TD period. One subject (GT) demonstrated a P waveform during the R2 period which changed to a P_{FS} waveform during the TD period (Figure 6.7B), another (RC) changed from a dual waveform (R2) to a pseudo-cycloid (PC) (TD) (Figure 6.10a), and the third (MH) demonstrated a dual jerk waveform during the R2 period which changed to a pendular with foveating saccades (P_{FS}) during the TD period (Figure 6.10b).

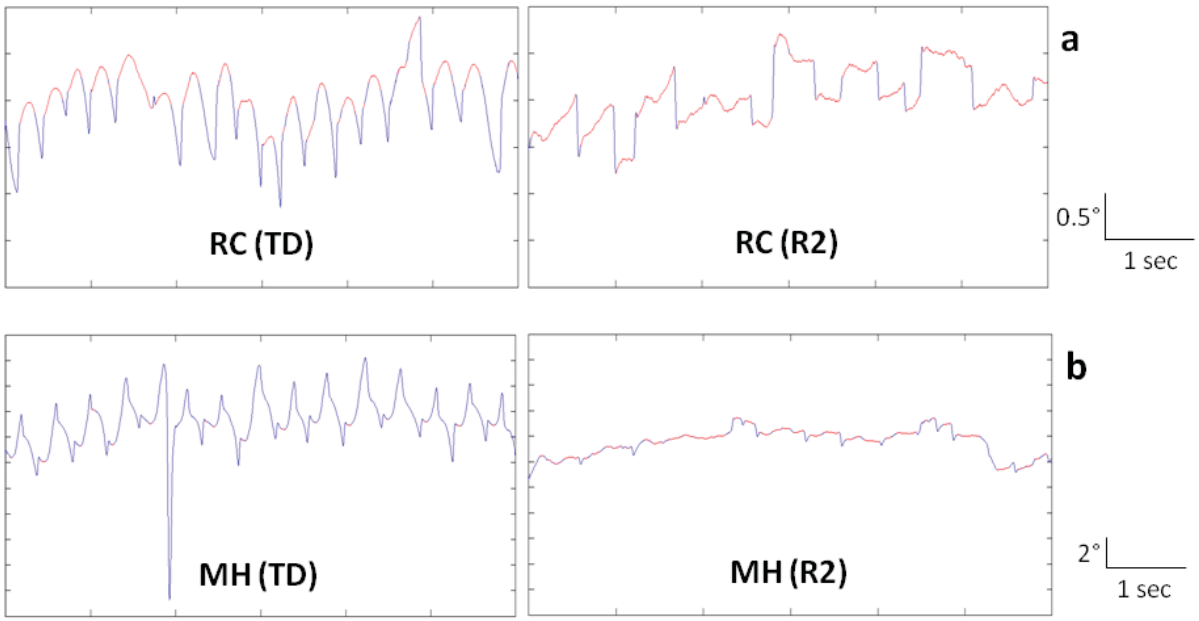

Figure 6.10: Change in predominant waveform for (a) RD and (b) MH during the TD and R2 periods. Individual scales are shown alongside each image. TD - "Task Demand" period, R2 - Second relaxed period

6.3.3 Stressful tasks and visual function

The median VA during the R2, TD and AA periods for subjects with nystagmus was 0.34, 0.39 and 0.39 LogMAR, respectively. Statistical analysis using the Wilcoxon matched pairs tests shows no significant difference in the TD and AA periods when compared to R2 (p = 0.981, and p = 0.528, respectively). This was unexpected as the foveation duration per cycle significantly reduced during the TD period. We would therefore expect to see a reduced VA during this time (Figure 6.11). Control subjects also demonstrated no significant change in VA during the TD (median -0.04) and AA (median -0.02) periods when compared to the R2 period (median 0.02, p = 0.138 and p = 0.264, respectively) (Figure 6.11).

Response Time (RT) significantly increased during the TD period for both subjects with nystagmus (median increase 530ms, p = 0.002) and control subjects (median increase 250ms, p = 0.01) (Figure 6.12). A comparison of RT between the control group and those

with nystagmus revealed no significant difference for either the TD or R2 periods (p = 0.07 and p = 0.086 respectively).

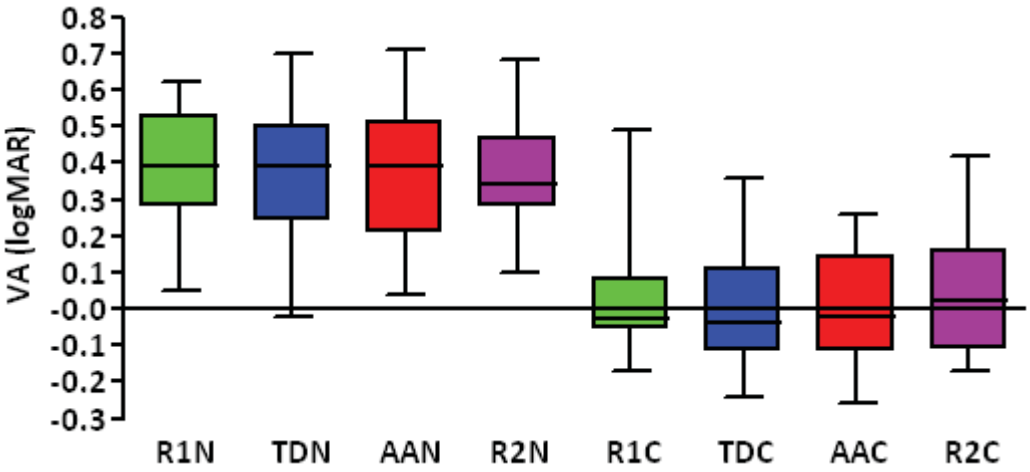

Figure 6.11: Median VA for control subjects and those with nystagmus for all periods. R1N - First relaxed period nystagmus, TDN - "Task Demand" period nystagmus, AAN - "Anticipatory Anxiety" period nystagmus, R2 - Second relaxed period nystagmus, R1C - First relaxed period controls, TDC - "Task Demand" period controls, AAC - "Anticipatory Anxiety" period controls, R2C - Second relaxed period controls

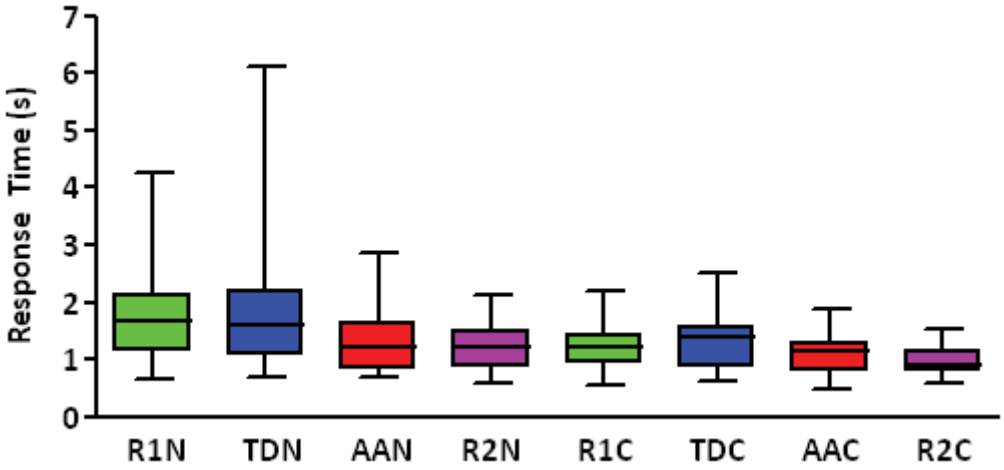

Figure 6.12: Median response times for control subjects and those with nystagmus for all periods. R1N - First relaxed period nystagmus, TDN - "Task Demand" period nystagmus, AAN - "Anticipatory Anxiety" period nystagmus, R2 - Second relaxed period nystagmus, R1C - First relaxed period controls, TDC - "Task Demand" period controls, AAC - "Anticipatory Anxiety" period controls, R2C - Second relaxed period controls

All of the data presented in this chapter so far, for which nonparametric statistics were used because the distributions were not normal, were subsequently analysed with parametric

tests after performing a log transformation to yield a normal distribution. The use of these more powerful tests did not result in any changes to the trends except for one instance and so the results of the more conservative non-parametric tests have been reported. However, in the case of the response time data, parametric statistical analysis indicated no significant difference between RT when comparing control subjects and those with nystagmus for the R2 period (unpaired t-test with Welch's correction for unequal variance 95% CI: -0.009 – 0.158, p = 0.079). However, the difference was significant when comparing the RT of control subjects and those with nystagmus during the TD period (95% CI: 0.003 – 0.249, p = 0.045) (Figure 6.13).

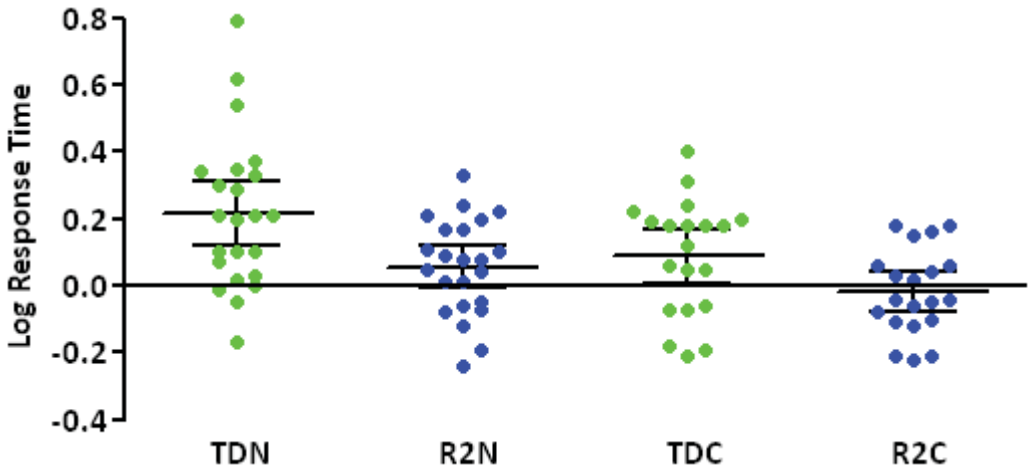

Figure 6.13: Mean of the Log response time for control subjects and those with nystagmus for the TD and R2 periods. Error bars represent 95% confidence intervals. TDN - "Task Demand" nystagmus, R2N - Second relaxed period nystagmus, TDC - "Task Demand" control, R2C - Second relaxed period control

Although the change in response time that we have seen is small, the log transform required to normalise the data results in a statistically significant result. This suggests, but does not prove, that such an increase in their response time is the reason that subjects with nystagmus report poorer vision when stressed.

6.4 Discussion

The results show that there was a significant increase in SkC during both the TD and AA periods, indicating that a prolonged state of arousal was created by the threat of electric shock. The SkC during the TD period being significantly higher than both AA and R2 indicates that this (TD) is the most stressful part of the experimental periods. This also indicates that people with nystagmus are more stressed by visual tasks that have a consequence (i.e. electric shock) attached to them. As with the investigation discussed in chapter 5, the use of the STAI questionnaire could possibly have added a further measure of anxiety. The drawback of using SkC as a measure of anxiety is that we do not have a specific scale for comparison. For example, an increase of 0.1µMho and 1.0µMho are both classed as simply an increase in SkC. We do not know whether either, in absolute terms, is classed as mild or high anxiety.

In agreement with Cham et al. (2008a), we found that stress has an effect on nystagmus waveform. Amplitude was significantly increased, which in turn increased intensity even though there was no significant change in frequency. On the other hand, for five of the subjects with nystagmus, a reduction in intensity was noted during the TD period. As with previous stressors, it appears that the TENS is not universally effective. As we did not actually increase the level of the TENS machine to double threshold during the TD and AA periods, it is possible that these subjects became aware of this and so were less stressed. In addition, two of the subjects who demonstrated a reduction in intensity during the TD period had used TENS machines in the past and were therefore familiar with the instrument. In this investigation, the waveforms were analysed by one experienced researcher. Ideally,

this would have been performed by two independent parties in order to remove any possible human/observer error.

With regards to the three subjects who exhibited a change in their predominant waveform when under stress, this could be an unconscious strategy to increase foveation in light of the increase in intensity. All of the subjects changed to a waveform with a higher number of saccades compared to their resting type. This could also be a compensatory mechanism by which the eyes re-foveate more often in an attempt to maintain the best possible VA.

This is the first investigation to specifically look at changes in VA related to stress in subjects with nystagmus using standard optotypes. The most important aspect of the nystagmus waveform when considering VA is perhaps the foveation period, the assumption being that the longer the foveation period, the better the VA (Dell'Osso and Daroff 1975; Dell'Osso et al. 1992; Erchul et al. 1998). In this investigation, the foveation was taken as the average foveation duration per cycle. The results showed a significant reduction in the time the eyes spent in the foveation window when under stress. This is in agreement with the findings of Cham et al. (2008a). Those previous studies that have provided evidence suggesting that VA critically depends on foveation length would therefore suggest that we should have seen a reduction in VA. However, although VA changed slightly during both TD and AA (median differences 0.01 and -0.01 LogMAR respectively), this decrease was not significant. With regards to the measurement of VA, a 4AFC staircase could have provided more accurate results especially as we have already shown that there is no difference between the VA thresholds for horizontally and vertically orientated Landolt C's. The staircase was extended for 2 mins following satisfaction of the criteria, i.e. 80 presentations and 8 reversals. This was done in order to maintain VA at threshold to better assess the effects of stress.

However, this could have caused some fatigue and/or a decrease in attention in the subjects. The use of a shorter time might have helped to counter these effects if they occurred.

As discussed earlier, many studies have also addressed the issue of "time to see" in relation to nystagmus. Wang and Dell'Osso (2007, 2009b) showed that subjects with INS take longer to fixate a target that has either jumped to a new position or been displaced in a smooth movement. We therefore included the measure of response time (RT) in our investigation. Our results show that those with nystagmus do not demonstrate a significant difference to control subjects during the R2 period. However, in the TD period, RT is significantly longer for those with nystagmus compared to controls. This suggests that the changes in the waveform and the consequent reduction in foveation could increase the time a subject needs to identify stimuli (i.e. achieve their best VA). We can therefore conclude that although VA is not affected as a result of stress, it is possible that subjects take longer to see the stimulus when there is a consequence related to their response.

It is interesting to note that there are significant changes in nystagmus waveform parameters during the TD period. In this task, there is a consequence (i.e. the threat of electric shock) linked to whether the subject can see the target. This can be related to how those with nystagmus see in real world situations. For example, if someone with nystagmus were late for a bus and was stressed because of this, then trying to read the bus numbers of a moving vehicle would require a longer time. This gives us a possible insight into the difficulties faced by those with nystagmus on a daily basis.

Further investigation is now needed in order to pinpoint more precisely why people with nystagmus report their vision to be worse when they are placed under stress. Although the

changes in response time have indicated a possible avenue of investigation, further investigation of these anecdotal reports is necessary.

Chapter 7: The Impact of Stress on Visual Function in Nystagmus: Self-Report Data

7.1 Introduction

As shown in the previous chapter, although the intensity of the waveform increases and foveation duration decreases, VA is not significantly affected by stress. That VA remains unchanged is at odds with anecdotal evidence from people with nystagmus who report their vision to be worse when stressed. Although the results obtained for response time may provide some explanation of this apparent discrepancy, the best source of information at this time remains the experience and observations of those who have nystagmus. It was therefore decided to use survey methods to question those with nystagmus about which situations they find stressful and how they feel their vision is affected, at those times.

There are many questionnaires that exist to assess stress/anxiety. The Manifest Anxiety Scale (MAS) takes items from the "Minnesota Multiphasic Personality Inventory" and is a measure of how anxious a person is at a given moment, i.e. a high score means someone is generally a very anxious person (Taylor 1953). Another questionnaire of this type is the "State and Trait Anxiety Inventory" (STAI) developed by Spielberger (1975). This questionnaire splits the measurement of anxiety into two categories: "state" – the feelings of anxiety triggered by the autonomic nervous system to a specific focus, and "trait" – how anxious a person is generally. However, although these questionnaires quantify the level of anxiety someone is feeling at a particular time, or how anxious a person is in general, they do not give any indication of the situations which create these feelings.

Questionnaires also exist that aim to assess self reported visual function. The most popular of these questionnaires are the National Eye Institute Visual Function Questionnaire (NEI-VFQ) and the VF-14. The NEI-VFQ (originally 51 items long) is designed to measure "vision targeted health related quality of life" (Mangione et al. 1998a). Over the years, it has been amended and shortened by many studies to 39 (Clemons et al. 2003), 25 (Ghazi-Nouri et al. 2006; Revicki et al. 2010), 9 or 8 items (Kodjebacheva et al. 2010). This questionnaire has been used to assess self reported visual function in eye disease such as optic neuritis (Cole et al. 2000), glaucoma (Jampel 2001), age related macular degeneration (ARMD) (Clemons et al. 2003; Revicki et al. 2010), as well as cataract and age related loss of visual acuity (Clemons et al. 2003). The NEI-VFQ has also been used as an outcome measure following ocular operations (Ghazi-Nouri et al. 2006). The VF-14 was designed by Steinberg et al. (1994) as a measure of visual function in patients with cataract. Similar to the NEI-VFQ, the VF-14 asks participants to grade their difficulty in performing everyday tasks such as driving and reading, etc. As well as to assess the visual function of patients with cataract both before and after surgery (Friedman et al. 2002), the VF-14 has been used to assess the impact of amblyopia (Sabri et al. 2006), glaucoma (Weisinger 2009), retinal disease (Linder et al. 1999), corneal disease (Fujita et al. 2005), and ARMD (Riusala et al. 2003), and as an outcome measure following penetrating keratoplasty (Ziakas et al.).

The VF-14 has also been used in nystagmus research by Pilling et al. (2005), who combined this with a social function (SF) questionnaire (derived from the NEI-VFQ and functional status questionnaire) in order to look at the correlation between visual and social function. The findings showed that those with nystagmus had low visual function, which was strongly correlated ($p < 0.001$) with reduced social function. Outcomes of treatment strategies in

nystagmus have also been measured with The VF-14 (McLean et al. 2007). More specific questionnaires have been used in nystagmus research to gain information regarding socioeconomic status (Wizov et al. 2002) and also subjects' experience of oscillopsia (Cham et al. 2008b).

These pre-existing questionnaires are unable to determine which situations people find stressful and exactly how this impacts on visual function in nystagmus. Hence it was necessary to construct a questionnaire that met our specific needs. To do this, it was necessary to first identify appropriate questions (items). This could be decided in a number of ways; clinical observation, focus groups or interviews (Streiner and Norman 1995).

Clinical observations are, as indicated by the name, observations of subjects by investigators and the items for the questionnaire are then based on their findings. However, as this is based on the knowledge and observational skills of those who do not have the condition or experienced the particular problem being investigated, there is a strong chance that biases can be introduced and/or mistakes can be made (Streiner and Norman 1995). For this reason, focus groups have been used extensively in the development of questionnaires (Mangione et al. 1998a; Berry et al. 2003; Boynton and Greenhalgh 2004; Ng-Mak et al. 2010). These involve selected groups of people who are representative of the target audience for the questionnaire. The researcher leads an open discussion on particular topics in order to gain insight into the important issues. Finally, interviews can be conducted in very much the same way as focus groups but on a one-to-one basis and can be either structured, semi-structured, or unstructured (Streiner and Norman 1995; Langdridge 2004). Data from focus groups and interviews can be collected via note taking, audio recording and/or video recording (Langdridge 2004). In the case of audio or video, the researcher then

reviews the recordings and produces a transcription. The transcripts are used to identify key issues and re-occurring themes. It is these issues and themes which are then used as the basis of items for the questionnaire (Streiner and Norman 1995; Mangione et al. 1998a). When dealing with focus groups and interviews, there are a number of considerations that need to be addressed. Interpersonal variables refer to the way in which a subject may respond differently depending on the interviewer's sex, ethnicity, and position (i.e. academic/researcher) (Langdridge 2004). Social desirability is also a factor that must be considered, being the term used to describe when subjects give their answers in order to appear in a more favourable light. Interpersonal variables and social desirability can be controlled for, in part, by using language that is understandable to all (i.e. no jargon) and by building a good rapport with the interviewee (Langdridge 2004).

Once the items have been identified, the questionnaire must be designed. There are two ways in which subjects can provide their responses: categorical or continuous. For categorical responses, subjects simply indicate with ticks or crosses which items apply to them, or answer yes or no, etc. (Streiner and Norman 1995). For continuous data, there are a number of scales that can be used, the most popular being the visual analogue scale (VAS) and the Likert scale (Figure 7.1a and b, respectively) (Guyatt et al. 1987; Streiner and Norman 1995).

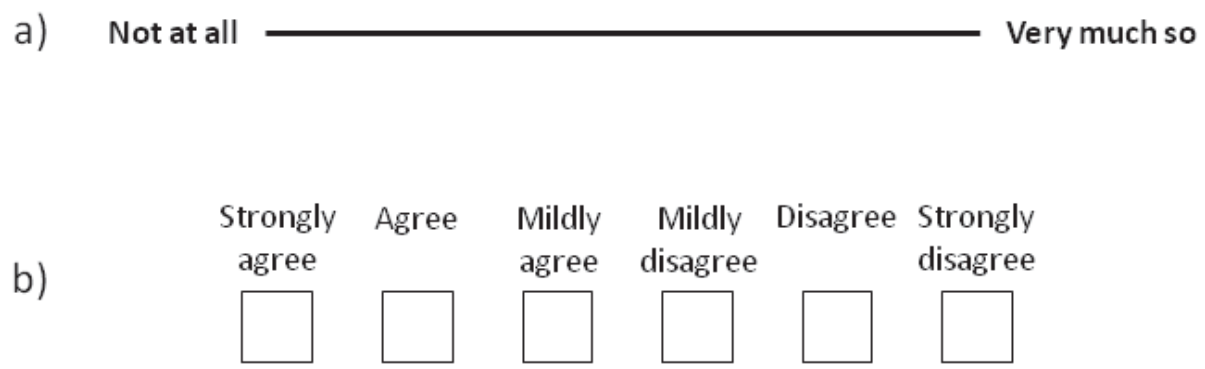

Figure 7.1: Examples of (a) the visual analogues scale (VAS) and (b) the Likert scale (Adapted from Streiner and Norman 1995)

With the Likert scale, the subject is required to indicate their agreement with a particular statement by ticking one of the individually labelled boxes (Figure 7.1b), whereas the VAS is a line (generally 10cm) upon which the subjects place a mark to indicate how they would rank their agreement. The VAS has wording at each end (anchors) with opposing statements (Figure 7.1a) (Streiner and Norman 1995). Although very different in their appearance, the two scales are comparable in their outcomes (Guyatt et al. 1987). The VAS is generally deemed to be the simpler of the scales to use (Streiner and Norman 1995), although some studies have found that subjects learn to use the Likert scale more easily (Guyatt et al. 1987; Streiner and Norman 1995).

Once the questionnaire is designed, it must be piloted so as to make sure that the questions are worded in a clear and concise manner (Streiner and Norman 1995; Mangione et al. 1998b). Questionnaires can also be analysed statistically for their reliability and validity as well as to predict how well certain items work in providing the information needed. Item response theory is an analysis based on the fact that each item focuses on a specific condition or change, and that the probability of someone answering this positively is unrelated to whether they will answer any other item positively. This ensures that the items

used in the questionnaire are the ones that give the best discrimination between respondents. One model for performing this type of analysis is the Rasch model (Streiner and Norman 1995), but this analysis is only necessary when constructing a questionnaire that attempts to measure a single latent trait e.g. anxiety. However, as the questionnaire to be developed here is being created solely for the purpose of acquiring specific information, this type of analysis is unnecessary.

The main aims of this investigation are:

- To design a questionnaire to investigate how people with nystagmus perceive their vision to be affected when under stress.
- To use this questionnaire to establish the main situations people with nystagmus find stressful, and how they feel their vision is affected.

7.2 Methods

Initially, members of the cohort were invited to take part in semi-structured one-to-one interviews. The first 10 subjects with nystagmus who responded took part (the interview schedule can be found in Appendix VIa). In order to reduce the effects of interpersonal variables and social desirability, all interviews were conducted in private by the lead investigator, whom all subjects had met before. Each volunteer was asked open questions about what situations they found to be most stressful. For each of the situations identified by the subjects, questions were then asked about how they felt their vision was affected at that time. With the subjects' permission, the interviews were recorded, transcribed and read through in order to identify the different stressful situations and the visual consequences of stress indicated by the subject (this was performed with the assistance of a

summer research student). All the themes that were identified in the interviews were included as items in the questionnaire. In total, nine stressful situations and seven visual consequences of stress were included.

The outcomes of the interviews were then used to construct a questionnaire that would be sent by post to subjects (see Appendix VIa for questionnaire). The questionnaire first asked subjects if they knew of any visual conditions that were associated with their nystagmus, in order to identify those subjects with acquired nystagmus, INS or FMNS. Subjects were then asked to provide a measure of their VA. A photocopy of a LogMAR chart calibrated for four metres was included with the questionnaire, and instructions given for subjects to measure their VA. The questions pertaining to the stressful situations and visual consequences of stress were separated into two sections. For each question, subjects indicated their answers by placing a mark on a visual analogue scale (VAS), consisting of a 10cm long line, ranging from “not at all” to “very much so”. For the questions asking about the visual consequences of stress, subjects were asked to answer in the context of the most stressful of these situations. At the end of the section regarding the stressful situations, as well as the visual consequences, subjects had the opportunity to add any point that they felt had been omitted.

Six hundred questionnaires were sent to members of the Nystagmus Network (NN) mailing list. After the return of those questionnaires sent to NN members, 160 questionnaires were distributed to control subjects in order to try to equal the number of returns from subjects with nystagmus (attempts were made to age match the respondents). Control subjects were made up of staff and students of the School of Optometry and Vision Sciences as well as friends and family of the investigator.

For each of the returned questionnaires, the position of the mark on the VAS scale for each question was measured using a ruler. The scale was read to the nearest millimetre (mm); since the VAS scale was 10cm in length, a mark placed at 10cm was given a score of 100. These values were then entered into a spreadsheet, and descriptive statistics were performed in order to show which of the situations and visual consequences had the highest median score.

7.3 Results

7.3.1 Interview results

The interviews identified nine situations that caused feelings of stress, namely: finding your way around an unknown place (Unknown Place), meeting new people (Meeting People), finding products on a shelf in a supermarket (Supermarket), crossing a road in heavy traffic (Crossing Road), finding a person in a crowd (Finding Person), pressure at work/university/college (Pressure), exams/studying (Exams), being late for something (Being Late), and speaking in public (Public Speaking). Below is an example of a response from a subject.

"So as I walked into the hotel, whereas if somebody with normal sight would walk in they could pick someone out and go and start chatting to them I sort of stand there alone"

Seven visual consequences of stress were identified as follows: difficulty seeing details / facial features (Facial Detail), things won't stay still long enough for me to see them (Won't Stay Still), everything blends into one (Blends Into One), I take longer to see things (Take Longer to See), things become blurred / defocused (Blurred), I can't focus on anything (Can't

Focus), and things appear to move (Things Move). Below is an example of a response given by a subject when questioned about the effects of stress on vision.

"And it takes me longer to read things which normally I could read quite quickly"

7.3.2 Questionnaire results

Of the 600 questionnaires that were sent out to the NN mailing list, only 164 were returned. This yielded a return rate of 27%. This is below the average response rate of around 60% seen in the literature (Gilmore et al. 2005; Baldwin et al. 2009; Spaar et al. 2009), however the membership of the NN is made up of academics, clinicians and parents of young children with nystagmus, not just those with nystagmus themselves. In fact, 10 questionnaires were returned accompanied by letters explaining that the NN member was a parent of a child who was too young to complete the questionnaire. The NN had no means of identifying the proportion of people on their mailing list who in fact had nystagmus. Of the 160 control questionnaires, 103 were returned, yielding a response rate of around 64%. The data in this investigation were not normally distributed (Shapiro-Wilk test for normality) and so all information was analysed in terms of median and inter-quartile ranges. Of the 164 respondents with nystagmus, 132 gave information regarding their age (median 31.50, inter-quartile range 15.00 to 53.00). VA data were returned by 151 of the subjects with nystagmus (median 0.5, inter-quartile range 0.4 to 0.7). Of the 103 controls, 99 gave information regarding their age (median 27.00, inter-quartile range 22.00 to 40.00). VA data were obtained from 102 of the control subjects (median -0.1, inter-quartile range -0.1 to 0.0).

7.3.2.1 Stressful situations

A table showing the scores for each question for each respondent can be found in Appendix VIb. People with nystagmus appeared to rate most of the situations as more stressful than the control group, with only three exceptions: “speaking in public”, “being late for something”, and “exams/studying” (Figure 7.2 and table 7.1).

Statistical comparison of the control and nystagmus groups using the Kruskal-Wallis test shows that the control group demonstrated a significantly higher score for only one situation (“Being late for something”) (Table 7.1). On the other hand, subjects with nystagmus had significantly higher scores than controls for the following situations:

- Finding your way around an unknown place
- Meeting new people
- Finding products on a shelf in the supermarket
- Crossing roads in heavy traffic
- Finding a person in a crowd

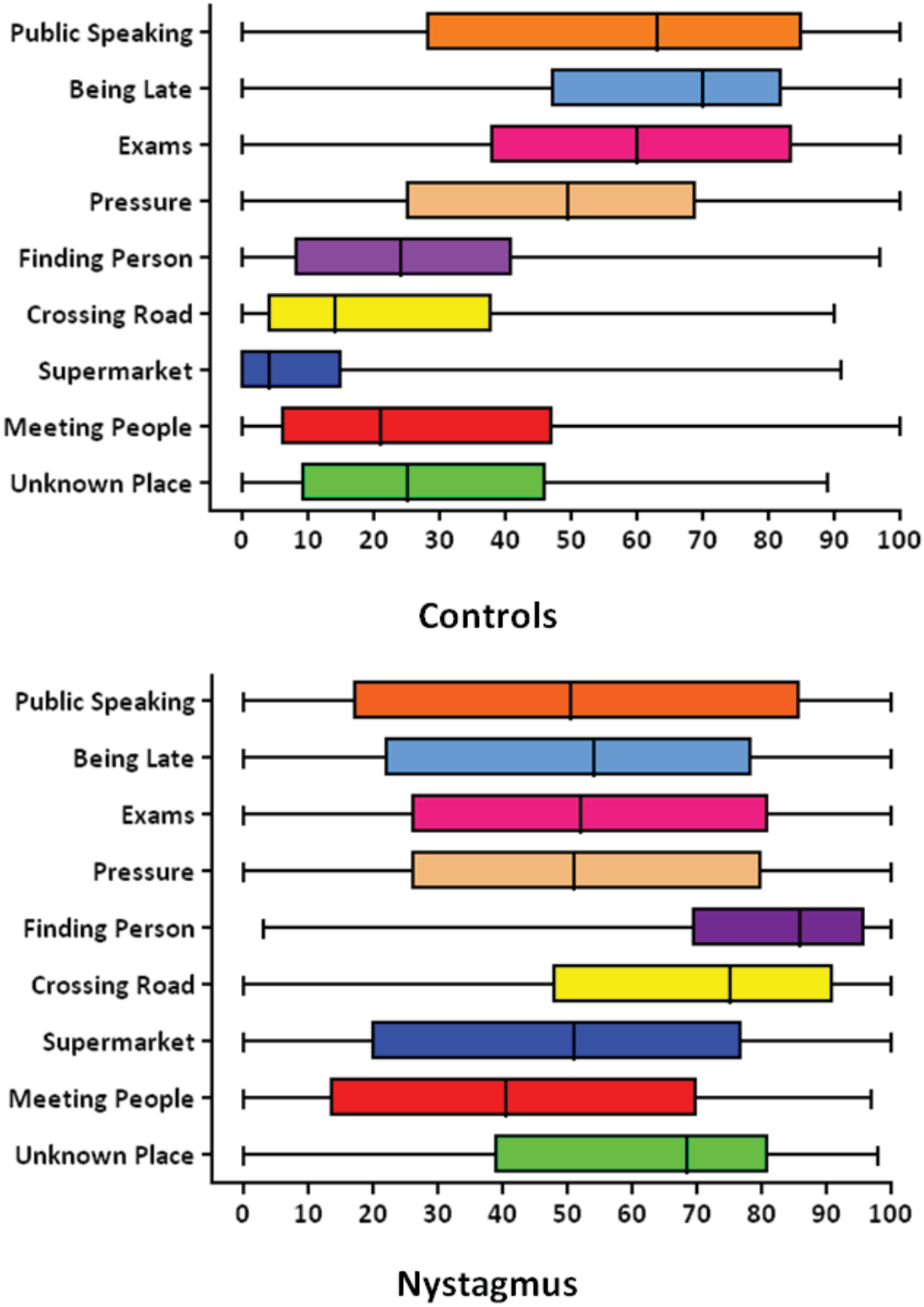

Figure 7.2: Response score for each of the stressful situations for both controls and those with nystagmus. Public Speaking - Speaking in public, Being Late - Being late for something, Exams - Exams/studying, Pressure - Pressure at work/university/college, Finding person - Finding a person in a crowd, Crossing road - Crossing roads in heavy traffic, Supermarket - Finding products on a shelf in a supermarket, Meeting people - Meeting new people, Unknown place - Finding your way around an unknown place

Situation	Median (Inter-quartile range) Controls	Median (Inter-quartile range) Nystagmus	Kruskal-Wallis
Public speaking	63.0 (28.0-85.0)	50.5 (17.0-86.0)	$p = 0.129$
Being late	70.0 (47.0-82.0)	54.0 (22.0-78.5)	$p < 0.05$
Exams	60.0 (38.0-83.5)	52.0 (26.0-81.0)	$p = 0.133$
Pressure	49.5 (25.0-69.0)	51.0 (26.0-80.0)	$p = 0.183$
Finding person	24.0 (8.0-41.0)	86.0 (69.5-96.0)	$p < 0.001$
Crossing road	14.0 (4.0-38.0)	75.0 (48.0-91.0)	$p < 0.001$
Supermarket	4.0 (0.0-15.0)	51.0 (20.0-77.0)	$p < 0.001$
Meeting people	21.0 (6.0-47.0)	40.5 (13.5-70.0)	$p < 0.001$
Unknown place	25.0 (9.0-46.0)	68.5 (39.0-81.0)	$p < 0.001$

Table 7.1: Median (inter-quartile ranges) values in response to the questions about stressful situations for control subjects and those with nystagmus. Comparisons made using Kruskal-Wallis test

7.3.2.2 Visual consequences of stress

For the section of the questionnaire regarding the visual effects of stress, the respondents were asked to think of the situation that they had scored as being the most stressful. As might be expected, the results (shown in figure 7.3) showed more extensive differences between those with nystagmus and the control group. Thus, controls did not have a median score of greater than 10 for any visual changes, whereas subjects with nystagmus showed a significantly higher score for all the identified visual effects of stress (Table 7.2).

The three highest scores were for: “things become blurred/defocused”, “I take longer to see things”, and “difficulty seeing details/facial features”. No significant difference was found between “difficulty seeing details/facial features” and “I take longer to see things”. However, both of these were significantly higher than all of the other visual consequences

when tested using a Kruskal-Wallis test with Dunn's Multiple comparison test: "things become blurred / defocused" ($p < 0.01$), "things won't stay still long enough for me to see them" ($p < 0.001$), "everything blends into one" ($p < 0.001$), "I can't focus on anything" ($p < 0.001$), "things appear to move" ($p < 0.001$).

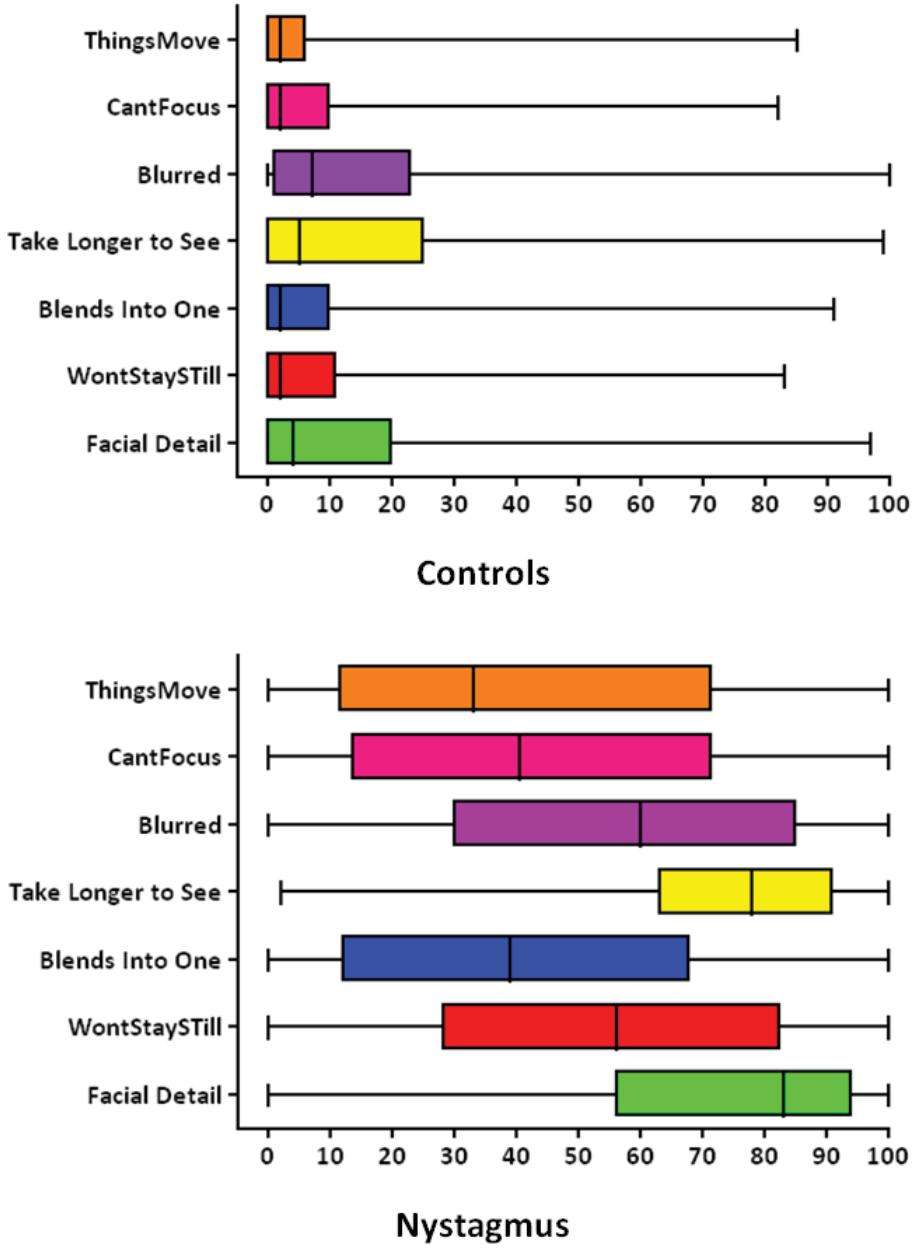

Figure 7.3: Response score for each of the stressful situations for both controls and those with nystagmus. Things Move - Things appear to move, Can't Focus - I can't focus on anything, Blurred - Things become blurred/defocused, Take longer to see - I take longer to see things, Blends into one - everything blends into one, won't stay still - Things won't stay still long enough for me to see them, Facial detail - Difficulty seeing details/facial features

Visual consequence	Median (Inter-quartile range) Controls	Median (Inter-quartile range) Nystagmus	Kruskal-Wallis
Facial detail	4.0 (0.0-20.0)	83.0 (56.0-94.0)	p <0.001
Won't stay still	2.0 (0.0-11.0)	56.0 (28.0-82.5)	p <0.001
Blends into one	2.0 (0.0-10.0)	39.0 (12.0-68.0)	p <0.001
I take longer to see	5.0 (0.0-25.0)	78.0 (63.0-91.0)	p <0.001
Blurred	7.0 (1.0-23.0)	60.0 (30.0-85.0)	p <0.001
Can't focus	2.0 (0.0-10.0)	40.5 (13.5-71.5)	p <0.001
Things move	2.0 (0.0-6.0)	33.0 (11.5-71.5)	p <0.001

Table 7.2: Median (inter-quartile ranges) values in response to the questions about visual consequences for control subjects and those with nystagmus. Comparisons made using Kruskal-Wallis test

To determine the relationship between the average score for the stressful situations and the average score for the visual consequences of stress, a regression analysis was performed, which demonstrated a highly significant relationship ($p < 0.001$) (Figure 7.4).

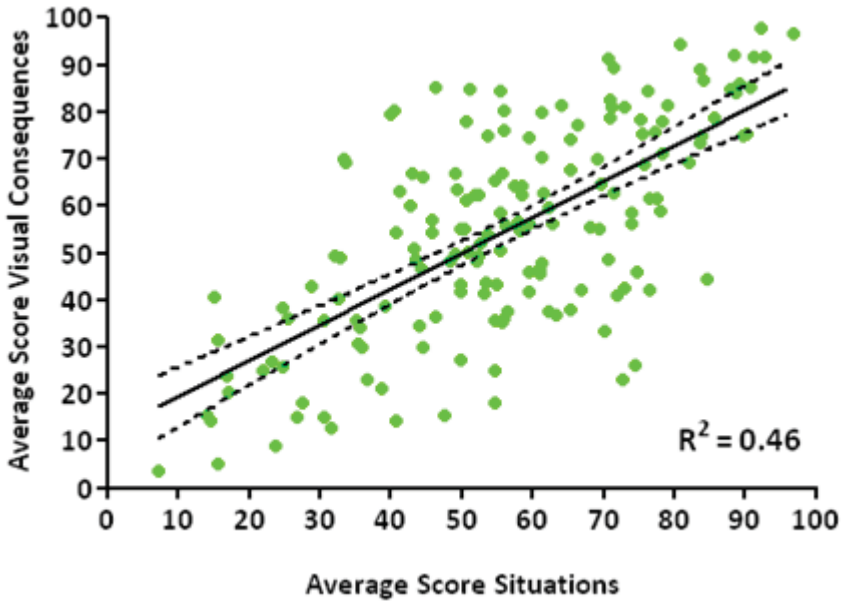

Figure 7.4: Linear regression of the average score for the stressful situations against the average score for the visual consequences

Similarly the average score for the stressful situations and the visual consequences were both significantly correlated with visual acuity of the individual subjects ($p < 0.001$ for both) (Figure 7.5). In contrast, regression of these same parameters against a subject's age, revealed no significant relationship ($p = 0.140$ and 0.301, respectively) (Figure 7.6).

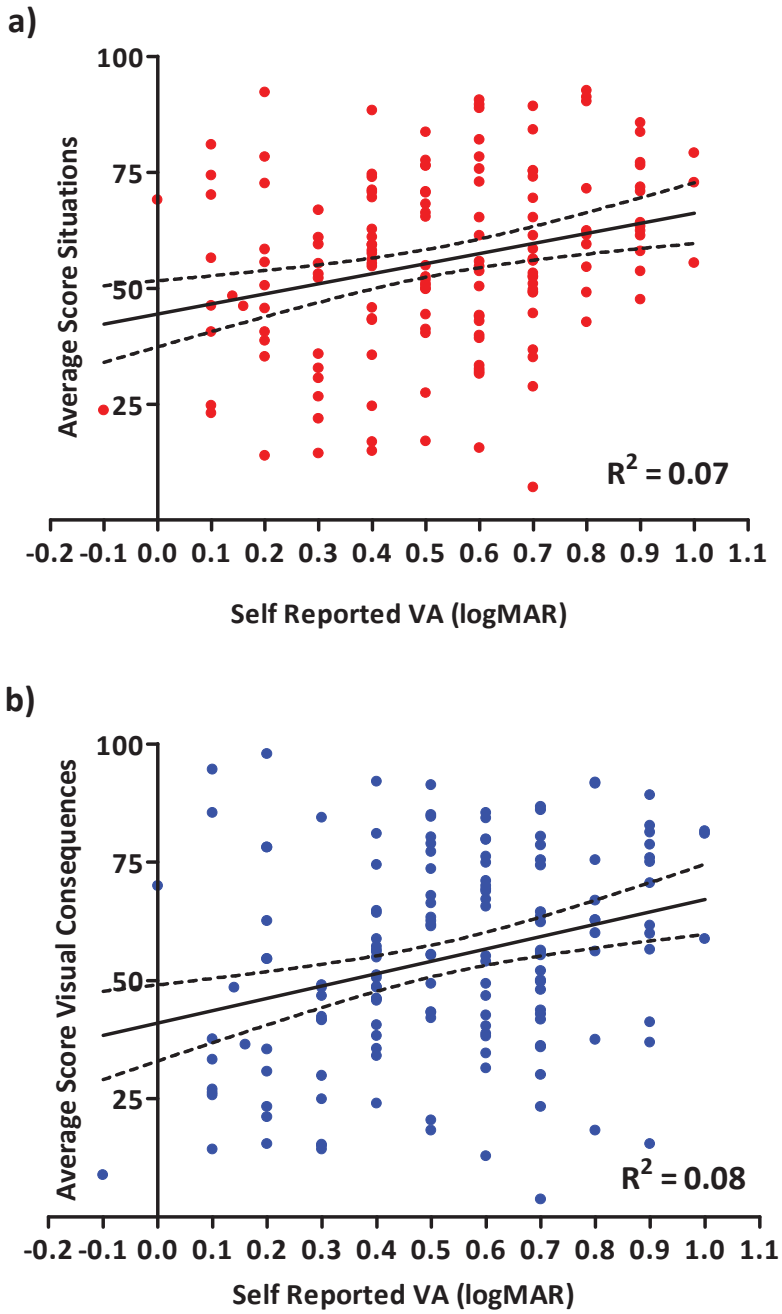

Figure 7.5: Linear regression of the average VAS score for a) stressful situations and b) visual consequences against VA (LogMAR) for subjects with nystagmus

Tables 7.3 and 7.4 show the results of correlation analysis for control and nystagmus subjects respectively. Each item of the questionnaire was correlated to every other item using the Spearman correlation coefficient. From these correlations we can see (from the control data) that some of the questions are similar or related in terms of what they aim to discover. The fact that all of the questions are significantly correlated in the subjects with nystagmus (with the exception of “meeting people” and “things won’t stay still”) suggests that, if those with nystagmus find one situation stressful, they may find others stressful also, whereas this is not entirely true in the control subjects. This seems understandable if one considers that when those with nystagmus find their vision is made worse in one situation, they are more likely to report worsening in other situations as well. The correlations also show that, if those with nystagmus report that their vision is made worse in one particular way (i.e. “I take longer to see things”), then they are more likely to report other visual consequences as well.

Although this does not affect the validity of our findings, these analyses do indicate that the questionnaire could be shortened by using only the questions that do not correlate (in the control group) if it were to be used again in the future.

		Unk	MP	Sup	CR	FP	Pr	Ex	BL	PS	FD	WSS	BIO	TLS	BLUR	CF	TM
Unk	Corr Coef	1.000	.391(**)	.289(**)	.288(**)	.415(**)	0.108	-0.026	0.076	0.174	.207(*)	0.184	0.152	.248(*)	0.174	0.177	.240(*)
	p		0.000	0.003	0.003	0.000	0.285	0.800	0.445	0.079	0.036	0.063	0.127	0.012	0.078	0.073	0.015
MP	Corr Coef	.391(**)	1.000	.296(**)	.298(**)	.346(**)	0.122	-0.012	-0.007	.379(**)	.239(*)	.318(**)	.243(*)	.247(*)	.212(*)	.200(*)	.302(**)
	p	0.000		0.002	0.002	0.000	0.227	0.906	0.946	0.000	0.015	0.001	0.013	0.012	0.031	0.043	0.002
Sup	Corr Coef	.289(**)	.296(**)	1.000	.385(**)	.409(**)	0.034	-0.091	.219(*)	0.111	.257(**)	.290(**)	.238(*)	.369(**)	.307(**)	.272(**)	.214(*)
	p	0.003	0.002		0.000	0.000	0.739	0.374	0.026	0.266	0.009	0.003	0.016	0.000	0.002	0.005	0.030
CR	Corr Coef	.288(**)	.298(**)	.385(**)	1.000	.571(**)	0.117	0.013	.224(*)	0.033	0.092	0.098	0.077	0.105	0.050	0.031	0.064
	p	0.003	0.002	0.000		0.000	0.245	0.898	0.023	0.739	0.353	0.323	0.440	0.292	0.619	0.759	0.518
FP	Corr Coef	.415(**)	.346(**)	.409(**)	.571(**)	1.000	.229(*)	0.001	0.028	0.064	0.152	.201(*)	0.019	.207(*)	.201(*)	0.103	0.068
	p	0.000	0.000	0.000	0.000		0.022	0.995	0.779	0.524	0.125	0.042	0.845	0.036	0.042	0.301	0.492
Pr	Corr Coef	0.108	0.122	0.034	0.117	.229(*)	1.000	.565(**)	0.047	0.166	0.028	-0.182	-0.085	0.060	0.135	-0.072	-0.111
	p	0.285	0.227	0.739	0.245	0.022		0.000	0.643	0.098	0.780	0.069	0.401	0.552	0.181	0.478	0.271
Ex	Corr Coef	-0.026	-0.012	-0.091	0.013	0.001	.565(**)	1.000	0.193	.240(*)	0.050	-0.033	-0.066	-0.029	0.119	-0.078	-0.081
	p	0.800	0.906	0.374	0.898	0.995	0.000		0.058	0.018	0.626	0.751	0.518	0.777	0.244	0.446	0.429
BL	Corr Coef	0.076	-0.007	.219(*)	.224(*)	0.028	0.047	0.193	1.000	0.101	0.102	0.006	0.114	0.128	0.063	0.012	-0.090
	p	0.445	0.946	0.026	0.023	0.779	0.643	0.058		0.311	0.306	0.956	0.251	0.197	0.525	0.904	0.364
PS	Corr Coef	0.174	.379(**)	0.111	0.033	0.064	0.166	.240(*)	0.101	1.000	.215(*)	0.129	0.137	.244(*)	0.138	.234(*)	.203(*)
	p	0.079	0.000	0.266	0.739	0.524	0.098	0.018	0.311		0.029	0.194	0.169	0.013	0.165	0.017	0.040
FD	Corr Coef	.207(*)	.239(*)	.257(**)	0.092	0.152	0.028	0.050	0.102	.215(*)	1.000	.584(**)	.717(**)	.723(**)	.705(**)	.597(**)	.637(**)
	p	0.036	0.015	0.009	0.353	0.125	0.780	0.626	0.306	0.029		0.000	0.000	0.000	0.000	0.000	0.000
WSS	Corr Coef	0.184	.318(**)	.290(**)	0.098	.201(*)	-0.182	-0.033	0.006	0.129	.584(**)	1.000	.693(**)	.653(**)	.546(**)	.716(**)	.800(**)
	p	0.063	0.001	0.003	0.323	0.042	0.069	0.751	0.956	0.194	0.000		0.000	0.000	0.000	0.000	0.000
BIO	Corr Coef	0.152	.243(*)	.238(*)	0.077	0.019	-0.085	-0.066	0.114	0.137	.717(**)	.693(**)	1.000	.750(**)	.640(**)	.811(**)	.738(**)
	p	0.127	0.013	0.016	0.440	0.845	0.401	0.518	0.251	0.169	0.000	0.000		0.000	0.000	0.000	0.000
TLS	Corr Coef	.248(*)	.247(*)	.369(**)	0.105	.207(*)	0.060	-0.029	0.128	.244(*)	.723(**)	.653(**)	.750(**)	1.000	.718(**)	.721(**)	.663(**)
	p	0.012	0.012	0.000	0.292	0.036	0.552	0.777	0.197	0.013	0.000	0.000	0.000		0.000	0.000	0.000
BLUR	Corr Coef	0.174	.212(*)	.307(**)	0.050	.201(*)	0.135	0.119	0.063	0.138	.705(**)	.546(**)	.640(**)	.718(**)	1.000	.631(**)	.581(**)
	p	0.078	0.031	0.002	0.619	0.042	0.181	0.244	0.525	0.165	0.000	0.000	0.000	0.000		0.000	0.000
CF	Corr Coef	0.177	.200(*)	.272(**)	0.031	0.103	-0.072	-0.078	0.012	.234(*)	.597(**)	.716(**)	.811(**)	.721(**)	.631(**)	1.000	.800(**)
	p	0.073	0.043	0.005	0.759	0.301	0.478	0.446	0.904	0.017	0.000	0.000	0.000	0.000	0.000		0.000
TM	Corr Coef	.240(*)	.302(**)	.214(*)	0.064	0.068	-0.111	-0.081	-0.090	.203(*)	.637(**)	.800(**)	.738(**)	.663(**)	.581(**)	.800(**)	1.000
	p	0.015	0.002	0.030	0.518	0.492	0.271	0.429	0.364	0.040	0.000	0.000	0.000	0.000	0.000	0.000	

Table 7.3: Table showing the Spearman correlation coefficients of all questionnaire items compared to one another for control subjects. Unk - Unknown Place, MP - Meeting People, Sup - Supermarkets, CR - Crossing Road, FP - Finding Person, Pr - Pressure, Ex - Exams, BL - Being Late, PS - Public Speaking, FD - Facial Detail, WSS - Won't Stay Still, BIO - Blends Into One, TLS - Take Longer to See, BLUR - Blurred, CF - Can't Focus, TM - Things Move. Green colour indicates significant results, yellow indicates insignificant results. * indicates significance to the 0.05 level, ** indicates significance to the 0.01 level

		Unk	MP	Sup	CR	FP	Pr	Ex	BL	PS	FD	WSS	BIO	TLS	BLUR	CF	TM
Unk	Corr Coef	1.000	.456(**)	.536(**)	.458(**)	.517(**)	.232(**)	.196(*)	.314(**)	.228(**)	.333(**)	.351(**)	.342(**)	.280(**)	.359(**)	.348(**)	.366(**)
	p		0.000	0.000	0.000	0.000	0.004	0.015	0.000	0.003	0.000	0.000	0.000	0.000	0.000	0.000	0.000
MP	Corr Coef	.456(**)	1.000	.398(**)	.295(**)	.331(**)	.353(**)	.284(**)	.303(**)	.492(**)	.311(**)	0.148	.242(**)	.187(*)	.223(**)	.274(**)	.314(**)
	p	0.000		0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.059	0.002	0.017	0.004	0.000	0.000
Sup	Corr Coef	.536(**)	.398(**)	1.000	.522(**)	.502(**)	.295(**)	.315(**)	.298(**)	.301(**)	.447(**)	.449(**)	.446(**)	.402(**)	.444(**)	.397(**)	.510(**)
	p	0.000	0.000		0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000
CR	Corr Coef	.458(**)	.295(**)	.522(**)	1.000	.545(**)	.241(**)	.246(**)	.326(**)	.229(**)	.400(**)	.437(**)	.396(**)	.386(**)	.400(**)	.358(**)	.482(**)
	p	0.000	0.000	0.000		0.000	0.003	0.002	0.000	0.003	0.000	0.000	0.000	0.000	0.000	0.000	0.000
FP	Corr Coef	.517(**)	.331(**)	.502(**)	.545(**)	1.000	.340(**)	.393(**)	.337(**)	.275(**)	.505(**)	.393(**)	.337(**)	.352(**)	.354(**)	.358(**)	.414(**)
	p	0.000	0.000	0.000	0.000		0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000
Pr	Corr Coef	.232(**)	.353(**)	.295(**)	.241(**)	.340(**)	1.000	.652(**)	.203(*)	.403(**)	.333(**)	.321(**)	.281(**)	.337(**)	.476(**)	.522(**)	.356(**)
	p	0.004	0.000	0.000	0.003	0.000		0.000	0.013	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000
Ex	Corr Coef	.196(*)	.284(**)	.315(**)	.246(**)	.393(**)	.652(**)	1.000	.185(*)	.393(**)	.192(*)	.309(**)	.228(**)	.169(*)	.371(**)	.344(**)	.360(**)
	p	0.015	0.000	0.000	0.002	0.000	0.000		0.022	0.000	0.018	0.000	0.005	0.038	0.000	0.000	0.000
BL	Corr Coef	.314(**)	.303(**)	.298(**)	.326(**)	.337(**)	.203(*)	.185(*)	1.000	.278(**)	.289(**)	.333(**)	.181(*)	.404(**)	.173(*)	.246(**)	.325(**)
	p	0.000	0.000	0.000	0.000	0.000	0.013	0.022		0.000	0.000	0.000	0.022	0.000	0.028	0.002	0.000
PS	Corr Coef	.228(**)	.492(**)	.301(**)	.229(**)	.275(**)	.403(**)	.393(**)	.278(**)	1.000	.214(**)	.217(**)	.161(*)	.238(**)	.290(**)	.355(**)	.306(**)
	p	0.003	0.000	0.000	0.003	0.000	0.000	0.000	0.000		0.006	0.006	0.041	0.002	0.000	0.000	0.000
FD	Corr Coef	.333(**)	.311(**)	.447(**)	.400(**)	.505(**)	.333(**)	.192(*)	.289(**)	.214(**)	1.000	.412(**)	.321(**)	.542(**)	.436(**)	.448(**)	.313(**)
	p	0.000	0.000	0.000	0.000	0.000	0.000	0.018	0.000	0.006		0.000	0.000	0.000	0.000	0.000	0.000
WSS	Corr Coef	.351(**)	0.148	.449(**)	.437(**)	.393(**)	.321(**)	.309(**)	.333(**)	.217(**)	.412(**)	1.000	.499(**)	.472(**)	.565(**)	.575(**)	.566(**)
	p	0.000	0.059	0.000	0.000	0.000	0.000	0.000	0.000	0.006	0.000		0.000	0.000	0.000	0.000	0.000
BIO	Corr Coef	.342(**)	.242(**)	.446(**)	.396(**)	.337(**)	.281(**)	.228(**)	.181(*)	.161(*)	.321(**)	.499(**)	1.000	.277(**)	.500(**)	.419(**)	.446(**)
	p	0.000	0.002	0.000	0.000	0.000	0.000	0.005	0.022	0.041	0.000	0.000		0.000	0.000	0.000	0.000
TLS	Corr Coef	.280(**)	.187(*)	.402(**)	.386(**)	.352(**)	.337(**)	.169(*)	.404(**)	.238(**)	.542(**)	.472(**)	.277(**)	1.000	.441(**)	.483(**)	.398(**)
	p	0.000	0.017	0.000	0.000	0.000	0.000	0.038	0.000	0.002	0.000	0.000	0.000		0.000	0.000	0.000
BLUR	Corr Coef	.359(**)	.223(**)	.444(**)	.400(**)	.354(**)	.476(**)	.371(**)	.173(*)	.290(**)	.436(**)	.565(**)	.500(**)	.441(**)	1.000	.648(**)	.527(**)
	p	0.000	0.004	0.000	0.000	0.000	0.000	0.000	0.028	0.000	0.000	0.000	0.000	0.000		0.000	0.000
CF	Corr Coef	.348(**)	.274(**)	.397(**)	.358(**)	.358(**)	.522(**)	.344(**)	.246(**)	.355(**)	.448(**)	.575(**)	.419(**)	.483(**)	.648(**)	1.000	.528(**)
	p	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.002	0.000	0.000	0.000	0.000	0.000	0.000		0.000
TM	Corr Coef	.366(**)	.314(**)	.510(**)	.482(**)	.414(**)	.356(**)	.360(**)	.325(**)	.306(**)	.313(**)	.566(**)	.446(**)	.398(**)	.527(**)	.528(**)	1.000
	p	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	

Table 7.4: Table showing the Spearman correlation coefficients of all questionnaire items compared to one another for nystagmus subjects. Unk - Unknown Place, MP - Meeting People, Sup - Supermarkets, CR - Crossing Road, FP - Finding Person, Pr - Pressure, Ex - Exams, BL - Being Late, PS - Public Speaking, FD - Facial Detail, WSS - Won't Stay Still, BIO - Blends Into One, TLS - Take Longer to See, BLUR - Blurred, CF - Can't Focus, TM - Things Move. Green colour indicates significant results, yellow indicates insignificant results. * indicates significance to the 0.05 level, ** indicates significance to the 0.01 level

7.4 Conclusion

The results identify those activities that people with nystagmus find stressful, and the impact of these situations on visual function. Although the response rate was low, this could be due to the fact that not all members of NN have nystagmus themselves, or that some families include children who were too young to respond. Although this might have been addressed by sending out a second round of questionnaires, NN were not agreeable to this, as they restricted the number of mailings to their members each year.

7.4.1 Stressful situations

We have shown that people with nystagmus find situations more stressful, in general, than people without the condition. In particular, people with nystagmus rate situations with a higher visual demand (e.g. “Finding a person in a crowd”) as being the most stressful compared to control subjects who rate more general situations (e.g. being late for something) as being most stressful. This indicates the difference in the level of difficulty that subjects have with day to day activities as a result of nystagmus. This result is consistent with the findings of Pilling et al. (2005), i.e. that visual function correlates strongly with social function. The two highest scored stressful situations were “Finding a person in a crowd” and “Crossing a road in heavy traffic”, which those with normal sight would take for granted as not being especially challenging. In fact, these two situations were in the lowest four situations scored by the control group. The inclusion of “Crossing a road in heavy traffic” is interesting, as this could imply experiencing difficulty in judging the speed of moving objects or in the perception of motion. As discussed in chapter 6, Wang and Dell’Osso (2007, 2009b) investigated how long it takes people with nystagmus to fixate

moving objects. The most recent research (Wang and Dell'Osso 2009b) shows that the point during the nystagmus cycle at which a target moves has an effect on how quickly someone with nystagmus can fixate it. This suggests that perhaps those with nystagmus have difficulty in judging the speed of moving objects, something which is reported anecdotally. Linear regression of the average score for the stressful situations against the average score for the visual consequences reveals a significant relationship between the two, indicating that those people who find situations more stressful find their vision is affected more. However, this could also be interpreted that those who have more pronounced visual consequences in a given situation become more stressed. The significant relationship across subjects between both stressful situations and visual consequences with VA suggests that those subjects with a poorer VA would generally find situations more stressful, and suffer more with visual consequences of this.

7.4.2. Visual consequences

The questions regarding the visual effects of the stressful situations were designed to probe more deeply into the anecdotal reports of people with nystagmus that their “vision” becomes worse when they are stressed. Vision scientists, optometrists, ophthalmologists and other optical professionals tend to think first of VA when describing “vision”. However, to the lay person, “vision” can mean, in addition to VA, anything from contrast or quality of vision to speed of perception. As expected, the figures for the visual effects show a much larger difference between the subjects with nystagmus and those from the control group, than do the stressful situations. The median score for all the visual effects was only 5.29 for the control group and 55.36 for those with nystagmus. The median score of the visual effects shows poor correlation with VA and with age in both the control and nystagmus

groups. Of the visual effects listed in the questionnaire, the two highest scores for those with nystagmus were “I take longer to see things” and “Difficulty seeing details/facial features”. Of these, the highest was “Difficulty seeing details/facial features”. The finding that those with nystagmus score “I take longer to see things” supports the conclusions of the previous chapter in which subjects’ response times were found to be slightly increased when under stress. Further investigation into this area with the use of, for example, visual search tasks to probe the “time to see” effect in nystagmus would possibly provide further answers concerning how someone with nystagmus sees the world. We have already seen that the percentage of time spent in the foveation window is reduced when subjects are under stress (Chapter 6). The fact that frequency is not significantly increased during this time suggests that those with nystagmus may rely on temporal summation of these foveation periods and hence the need for a longer viewing time. This would have an impact on those with nystagmus in the real world where viewing time can often be restricted, e.g. trying to read a train timetable when it’s due to depart, or to see the number on a bus which is driving past. It has already been indicated that “time to see” could also be a useful outcome measure following treatment of nystagmus, at least in adults (Sprunger et al. 1997; Hertle and Reese 2007).

The visual effect scored highest by those with nystagmus was “Difficulty seeing detail/facial features”. The face is generally of low contrast, the nose, lips, ears and eye lids all being of a similar colour, and contrast sensitivity has been shown to be reduced in people with nystagmus for spatial frequencies higher than 1.5 cycles per degree (cpd) (Hertle and Reese 2007). This could be explained by a study from Burr and Ross (1982) which showed in normally sighted subjects that, at increased image velocities, the contrast sensitivity

function shifted towards lower spatial frequencies. The information we have gathered in this investigation suggests that viewing high spatial frequencies and low contrast images becomes more difficult when people with nystagmus are placed under stress. This could suggest that there is a change in a person's contrast sensitivity linked to the intensity of the nystagmus waveform. Therefore, in addition to motion perception, the effect of the nystagmus waveform on CS is an interesting avenue for further investigation into the effects of stress on nystagmus, in an effort to establish what leads those with nystagmus to report reduced vision in such situations.

In conducting this investigation, there were a number of possible limiting factors. During any interview process, we must consider the effects of "interpersonal factors" (the way in which subjects respond to the sex, ethnicity etc. of the interviewer) and "social desirability" (subjects giving responses in order to appear in a more favourable light) (Langdridge et al. 2004). In this investigation there was only a limited ability to control or minimise these effects; namely, the interviews were performed by the same researcher, whom all subjects had met previously.

The apparently low return rate from the questionnaire sent to subjects with nystagmus could be due to a number of factors. Prior to sending the questionnaire, it was not known at the time of the mailing that NN did not keep data that identified which members actually have nystagmus. As stated previously, some and possibly many members are parents of children with nystagmus or researchers. In light of this, which only subsequently became apparent, it may be that those recipients without nystagmus simply, but understandably, chose not to respond. Knowing the number of nystagmus subjects, who we could have expected to have returned the questionnaire, would have given us a more accurate idea of

the actual return rate. It would also have been ideal to send out a second round in order to try to increase the number of respondents, but this was not possible due to restrictions from NN who distributed the questionnaire for us.

Although we have shown that people with nystagmus have difficulty with certain tasks when they are stressed, the question arises as to whether this is true only for those with nystagmus, or also for those with some other visual impairment. This could be addressed by asking a group of people with a congenital visual impairment not linked to nystagmus to complete the questionnaire. However, the fact remains that when people with nystagmus are placed under stress, this impacts on their eye movements, which is likely to affect their visual performance, whereas the visual impairment in other subject populations will not be affected dynamically.

In conclusion, we have shown that people with nystagmus find visually demanding situations to be particularly stressful. In agreement with chapter 6, we have once again found that increased “time to see” is a possible reason why people with nystagmus report their vision becomes worse when under stress. These results suggest that people with nystagmus may have more difficulty perceiving fine detail and low contrast images when they are under stress.

Chapter 8: General Discussion and Future Work

8.1 General discussion

The main aim of the studies described in this thesis was to investigate the effects of stress on visual function in people with nystagmus. We began by examining the effects of different stimuli and their orientations on the measurement of VA. A stressor was then identified and validated before being used to create stress in people with nystagmus whilst simultaneously measuring their VA. Finally, we further investigated the changes in visual function with stress by using survey methods to question those with nystagmus directly about their experiences. The main conclusions drawn from each of the investigations have been discussed in the relevant chapter. The findings are summarised here.

In chapter 4, the issue of stimulus orientation and its effect on the VA of people with nystagmus was addressed. The aim of this investigation was to identify any differences in VA between horizontally and vertically orientated Landolt C and Tumbling E optotypes and to determine whether the VA measured with each optotype was comparable. Although the impact of orientation on grating acuity in nystagmus has been well documented, with subjects consistently having a poorer VA for vertical gratings, the research regarding optotype acuity is not so clear. The current literature on the orientation of optotypes and VA in people with nystagmus is both contradictory and devoid of statistical analysis (Chung and Bedell 1995; Pascal and Abadi 1995). In respect of the orientation of the Tumbling E optotype, to our knowledge this is the first investigation of the effect of orientation in subjects with nystagmus.

The results from 21 people with nystagmus show that, in agreement with previous investigations, subjects with nystagmus demonstrate a poorer VA for vertical gratings compared to horizontal. The data also showed that, for those subjects with nystagmus, there is no significant difference in the VA measured with the Landolt C or Tumbling E with either horizontal or vertical orientations. In addition, the investigation provided more robust data on the effects of orientation of Landolt C stimuli on VA in people with nystagmus. Surprisingly, control subjects for this investigation demonstrated a poorer VA for the vertically orientated Tumbling E stimuli. On the basis of this investigation, the horizontal Landolt C was chosen as the best stimulus for measuring VA in subsequent studies.

The next step was to identify an appropriate stressor. In chapter 5, we discussed the ideal features of a stressor to be used in subsequent research, which included allowing subjects to maintain fixation on the VA stimulus and creating a feeling of stress that is sustained throughout the duration of VA measurement using standard psychophysical methods. Because of the methods being employed in our investigations, namely a push button response box for VA measurement and electrodes placed on the fingers for skin conductance (SkC) measurement, the stressor must also allow the subject the use of both hands. From the literature, electric 'shock' (or the threat thereof) was identified as the best stressor that met all of the requirements, and the TENS machine was chosen as a safe and convenient way of administering electrical impulses. We presented data from 20 subjects without nystagmus and showed that the 'threat' of an electric shock generated a significantly higher, sustained SkC reading, thus indicating that a state of stress/arousal had been created.

Chapter 6 reports the results of the first study to specifically investigate the changes in visual function associated with stress for those with nystagmus. The only previous study had shown detrimental effects on the nystagmus waveform (Cham et al. 2008a), but that work was performed with subjects viewing the target at a distance and gaze angle that were not optimal for all subjects with nystagmus. We aimed to address the issue of visual function by measuring VA under optimal conditions as well as subject 'response time' to make the discrimination. Each subject performed 4 measures of VA. The first and fourth measures were performed without the use of the stressor (TENS machine) to yield "relaxed" data (the first measure being performed to reduce any learning effect). The TENS machine was used to create two different stressful situations: 'task demand' (TD), in which subjects were told that they would receive a burst from the TENS if they gave an incorrect response to the VA stimulus, and 'anticipatory anxiety' (AA) in which subjects were told they could receive a burst from the TENS at any time. In both stressful states, subjects were told that the TENS intensity would be double their threshold, although this was never actually the case.

The results showed that subjects' SkC was significantly higher during both stressful states compared to the second relaxed (R2) period, thus indicating that subjects were more stressed. SkC was also significantly higher in the TD period compared to AA, suggesting that this was the more stressful situation. In agreement with previous studies, we found that stress has a detrimental effect on the nystagmus waveform with an increase in amplitude and intensity (but not frequency) during the TD period compared to R2, and a decrease in foveation duration. It might be expected that, as foveation duration decreased, we would see a reduced VA. However, this was not the case. No significant difference was found in VA between any of the experimental periods. This might suggest that the eye movements

themselves have little impact on VA, presumably because an underlying amblyopia is present. This indicates the necessity for carrying out additional measures of visual function when examining patients with nystagmus. The changes in response time noted in this investigation indicated that both those with nystagmus and controls take longer to identify the stimulus when there is the threat of an electric shock. However, comparing the response times between control subjects and those with nystagmus, we found a significant difference between these two groups during the TD period but not during the R2 period. Moreover, although both groups demonstrated an increase in response time, this was higher for those with nystagmus. This change in response time could provide an indication of the effect of real world situations on a person's visual function. Although significant increases in response time were found, the changes reported were small. As a result, further investigation was required. For this, we used the best source of information regarding nystagmus, the subjects themselves.

Survey methods were used in chapter 7 in order to question those with nystagmus about how they felt their vision was affected when they were placed under stress. As a first step, semi-structured interviews with ten subjects were undertaken in order to identify the situations in which people felt most stressed and the way in which they felt their eyes (and vision) were affected in these situations. Based on the outcomes of this process, a questionnaire was then constructed and distributed to a large number of subjects to grade their agreement with each item using a visual analogue (VAS) scale. The results revealed that, compared to control subjects, those with nystagmus found situations with a visual dimension (i.e. "finding a person in a crowd", "crossing a road in heavy traffic" and "finding your way around an unknown place") to be the most stressful. With regards to changes in

vision experienced when under stress, people with nystagmus reported that they “take longer to see things” and have “difficulty seeing details and facial features”. The fact that subjects gave a higher score to “take longer to see things” over “things become blurred / defocused” lends support to the findings reported in chapter 6 (i.e. subject response time is increased when under stress). The highest scored visual problem was “difficulty seeing details and facial features”. This suggests an avenue for future research into changes in contrast sensitivity that might occur with stress. The situations reported as being more stressful also provide the basis for future research involving eye tracking studies of patients in everyday situations, such as catching a train/bus or looking for a person in a crowded place. The technology to achieve this aim has only recently become available and would allow a more realistic impression of a patient’s visual function and the difficulties experienced by people with nystagmus in the real world.

Further research investigating the VA of subjects with nystagmus using tests that aim to eliminate the effect of eye movements on perception would perhaps give some indication of the actual extent to which eye movements affect VA, and identify any underlying amblyopia. This would, in turn, indicate how much the vision of children with nystagmus is affected during the plastic period, and how we might aim to improve their visual capabilities by early intervention. With the advancements made in optical coherence tomography (OCT) imaging in recent years, further investigation with high speed SD-OCT would perhaps help to identify any, perhaps subtle, retinal changes in patients with a current diagnosis of idiopathic INS. The following sections of this chapter will outline two brief pilot studies, which were performed on a small number of subjects as a proof of concept in order to test their viability for future research.

8.2 OCT imaging and nystagmus

Optical Coherence Tomography (OCT) is a non invasive way of imaging the ocular tissues. Modern advancements in OCT imaging mean that images are taken in the spectral (Fourier) domain (SD-OCT). This facilitates the imaging of patients with nystagmus because SD-OCT records images at a very high frequency of 18,000 to 40,000Hz (Sakata et al. 2009). A single cross sectional image of the depth (axial depth) of the retina is known as an A-scan, and a series of A-scans can be taken in rapid succession and, when placed side by side, create a linear cross-section (B-scan) of the retina (Thomas and Duguid 2004; Chang and Budenz 2008). Recently, Cronin et al. (2009) undertook a prospective SD-OCT study to image the central retina of patients with nystagmus. This study commented on the usability of SD-OCT in order to detect the abnormal foveal morphology found in patients with nystagmus associated with albinism. Although the idiopathic subjects appeared to possess a fovea, no quantitative measurement of retinal features or morphology was performed (Cronin et al. 2009).

The study described here was undertaken as a pilot investigation of the foveal morphology of patients with idiopathic INS.

8.2.1 Methods

Four subjects with idiopathic INS were recruited from the RUN cohort. Using a wavelength of 1060nm (bandwidth 50-70nm), SD-OCT imaging of an 18° X 18° area around the fovea was performed on the RE. The readings consisted of 512 X 512 A-Scans, at a rate of 47,000 A-Scans/s (see Esmaeelpour et al. 2010 for more information regarding the instrument and methods employed).

8.2.2 Results

Images of each of the four subjects are shown in figure 8.1. Interestingly, when the series of scans from a given subjects is viewed transversely, it is possible to discern from the displacement of each scan that subject's nystagmus waveform type by observing the edge of the scans (Figure 8.2).

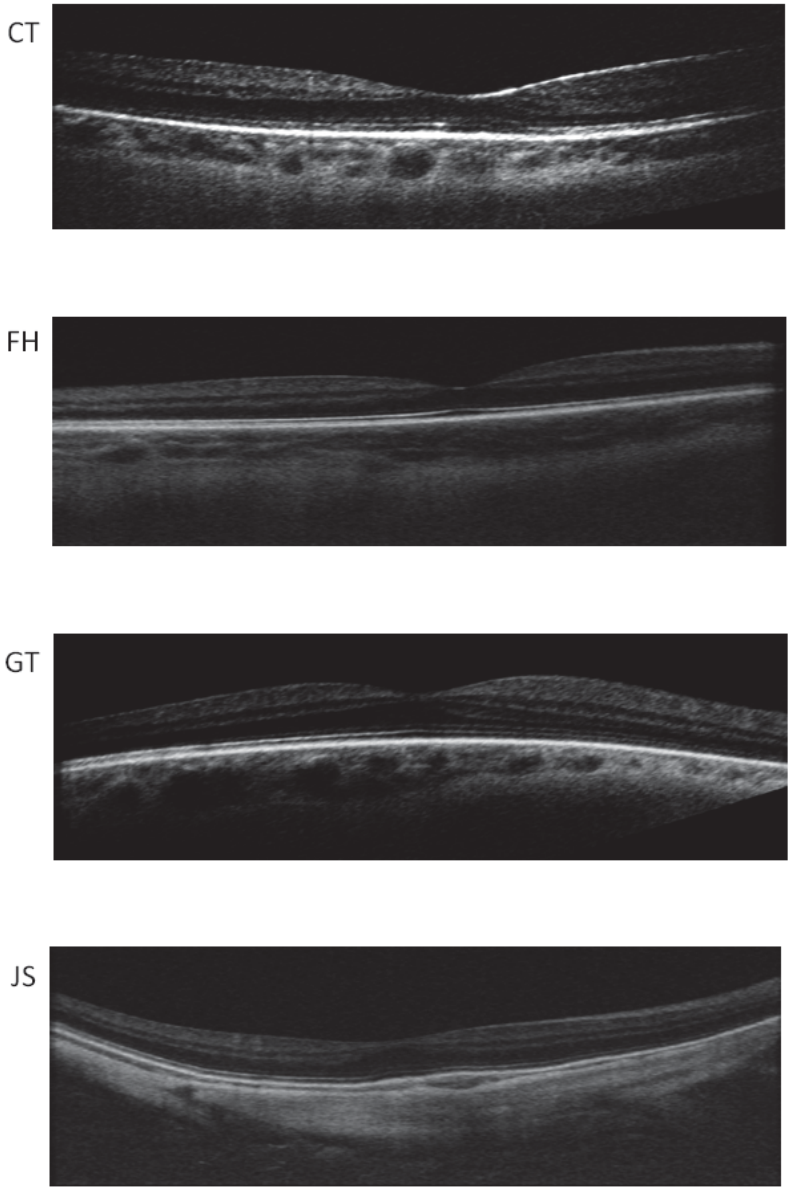

Figure 8.1: OCT images of the central fovea of four subjects with idiopathic INS

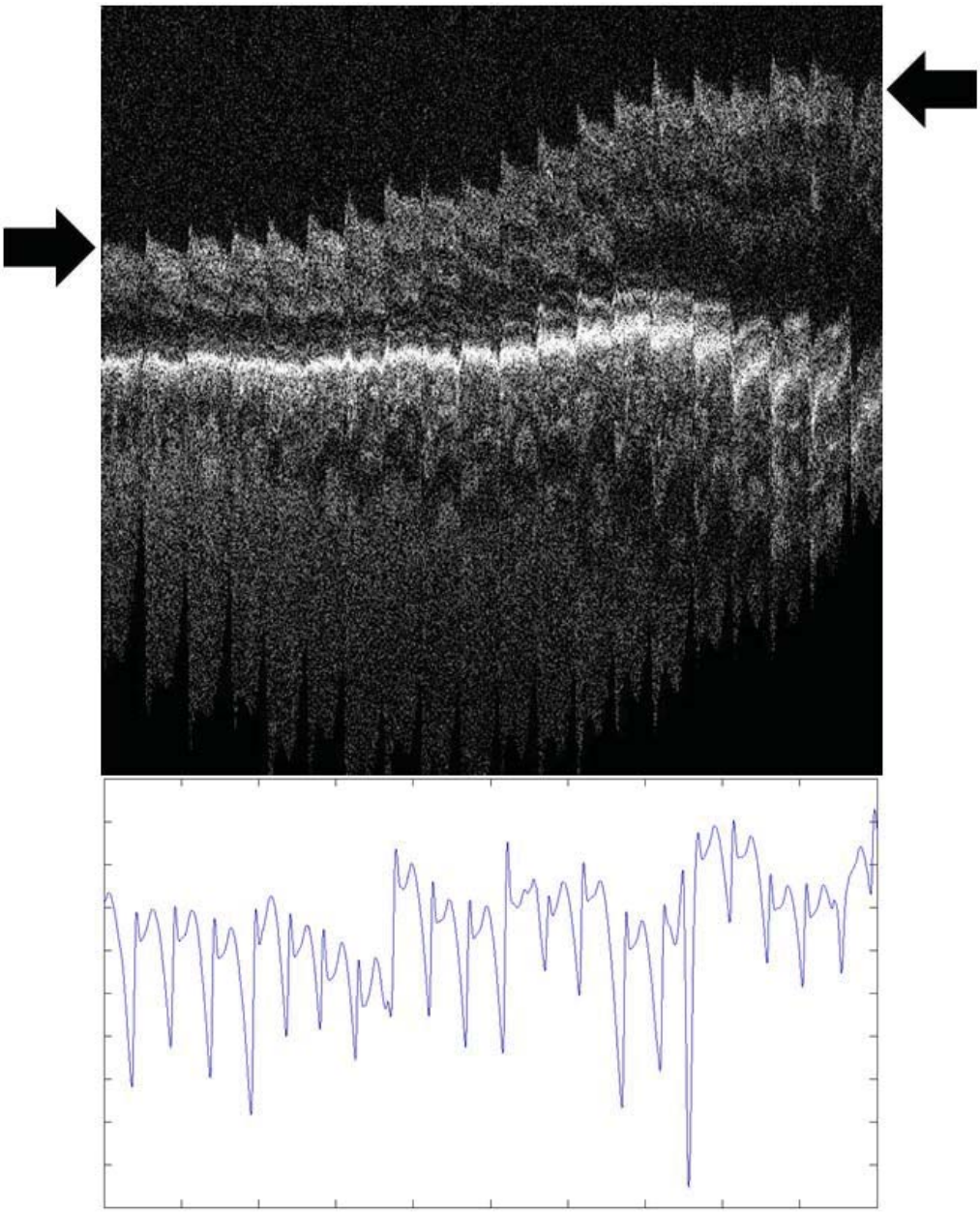

Figure 8.2: Upper figure: transverse view of OCT scans for subject GT in which the pattern of displacements (see arrows) appears to reflect the subject's waveform. Lower figure: waveform trace of the same subject obtained when this subject participated in the investigation described in chapter 6

8.2.3 Conclusions

This pilot study has shown that it is possible to obtain detailed images of the foveal area of those with nystagmus. With further investigation, and by obtaining additional measurements of axial length, it will be possible to correct for magnification and accurately measure the thickness of the different retinal layers. This would allow us, for the first time,

to obtain quantitative measurements for comparing foveal morphology of people with nystagmus with that in age, sex and axial length matched controls.

8.3: A new method for the measurement of VA

As was discussed in chapter 2, improved VA has been attributed to longer foveation. However, lengthening foveation duration later in life results in only a small improvement in VA. This suggests that amblyopia is present, meaning that any reduction of eye movements in later life can only have a minimal effect on VA. Previous studies to address this question have attempted to stabilise the retinal image in people with nystagmus (Abadi and Kingsmith 1979; Leigh et al. 1988). Leigh et al. (1988) found that the use of a para-foveal photoflash (directed at the subject's eyes) results in oscillopsia (see section 2.5) in subjects with nystagmus. Abadi and Kingsmith (1979) used brief presentations (0.2ms) of a stimulus (not a photoflash) in an attempt to minimise or eliminate the effects of eye movements but found a reduced sensitivity to grating stimuli. This follows Bloch's law in normal vision, and the work of Baron and Westheimer (1973), which showed that VA is affected by exposure duration to the stimulus. The pilot study described here uses a photoflash to stabilise the image of a moving grating in two control subjects, and demonstrates that stimulus motion is not a barrier to the measurement of VA.

8.3.1 Methods

A grating with a width of 0.66mm per cycle (VA: 0 LogMAR at 1m) was placed around a drum mounted on an optical bench (Figure 8.3a) and viewed through a 5cm diameter aperture with a fixation cross (Figure 8.3b).

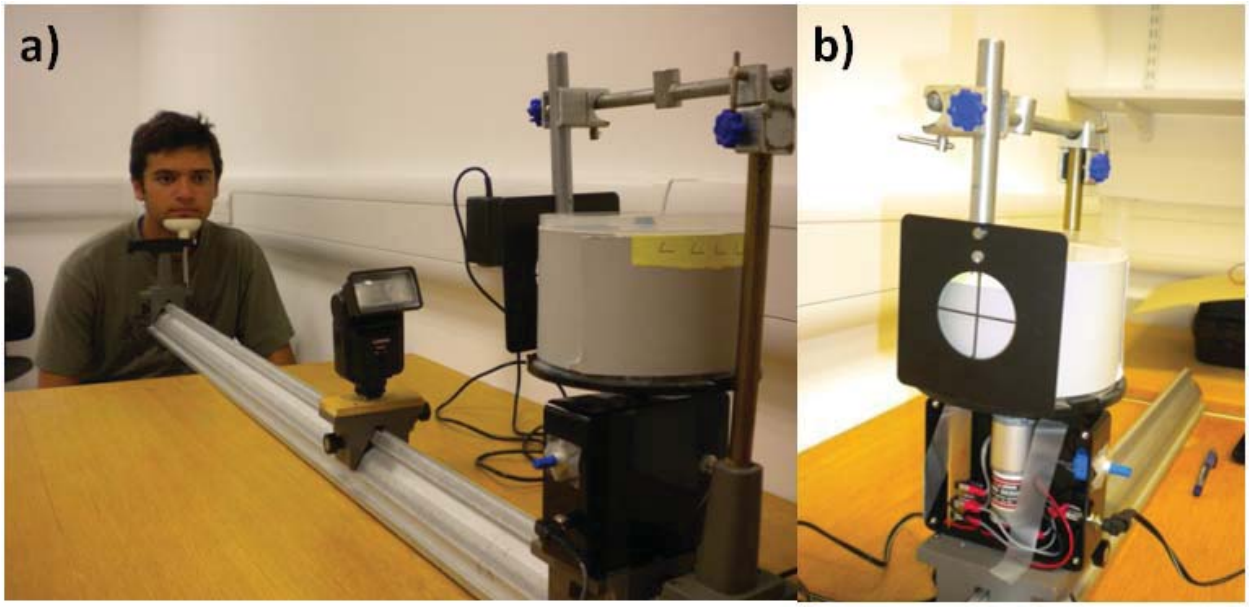

Figure 8.3: a) Subject sat in front of grating drum mounted on optical bench, b) Grating drum and aperture

The method of increasing and decreasing limits was used to measure VA using the drum when stationary. The distance between the subject and the drum was increased gradually until the subject reported it could not be resolved. The drum was then moved back towards the subject until the grating was visible again. Threshold was taken as the position where the subject was just able to resolve the grating. The drum was then rotated at 144°/s in order to blur the image across the retina (i.e. the grating was not visible at this speed). A photoflash (Cobra MD210) was used to illuminate the stimulus, and the subjects asked if they were able to resolve the grating. The stimulus was flashed three times at each distance used. If the answer was yes for two or more of the trials, then the distance between the drum and subject was increased; if the answer was no for two or more of the trials, then the drum was moved closer to the subject. No fixed step size was used. Threshold was taken as the position at which the subject was just able to resolve the grating.

8.3.2 Results

Two male subjects (without nystagmus) took part (PJ and MD). Subject's ages were 28 and 22, respectively. PJ was emmetropic (R: +0.25/-0.25 x 155, L: +0.75/-0.50 x 170) and wore no optical correction, MD was myopic (R: -2.00DS, L: -2.00DS) and wore full spectacle correction. Neither subject had any ocular pathology. The results are presented in table 8.1, and show no difference in the recorded VA between the two conditions (i.e. static vs moving grating).

ID	Distance Static	Distance Flash	MAR Static (minutes of arc)	MAR Flash (minutes of arc)	VA Static (LogMAR)	VA Flash (LogMAR)	Clinically measured LogMAR acuity
PJ	117.5	116.0	0.96	0.96	-0.02	-0.02	-0.10
MD	137.0	134.0	0.84	0.84	-0.08	-0.08	-0.10

Table 8.1: Results of VA testing with static and flashed stimuli. MAR - Minimum Angle of Resolution

8.3.3 Conclusions

This study indicates that brief flashes can be used to overcome retinal image motion with brief afterimages. Further investigation is now needed to improve this technique with more control subjects and the use of a more robust psychophysical technique. The use of the photoflash to "freeze" the image of a grating on the retina could then be applied to the testing of patients with nystagmus in order to eliminate the effects of eye movements on VA. The slightly poorer VA found with the drum compared to that found using a standard LogMAR chart could be down to a number of factors: the constant 5cm aperture of the stimulus, which could have had an impact at greater distances (because the viewable stimulus became smaller), the quality of the printed grating, and/or the technique used to measure VA.

8.4 Final remarks

Based on the work reported here as well as the work of others, it becomes clear that nystagmus is a highly variable condition. All parameters of the nystagmus waveform, as well as VA, CS, and refraction, have a large range. This makes nystagmus a challenging condition to study, partly because this variability means that patients cannot be compared directly to one another. A further compounding factor is that of stress/anxiety, to which responses are also highly variable. Some people become stressed or anxious very easily, whereas this is not the case for others. The results we have reported support the aptness of the quote at the beginning of this thesis:

"I've found it has little to do with the things you see and everything to do with the way you see them"

As yet, we still do not know how people with nystagmus "see" the world. People with nystagmus do not ever experience "normal" vision and so cannot describe the difference. With further research and the assessment of visual function beyond static VA, hopefully we can begin to construct a better idea of how they perceive the world. It is hoped that the work reported here has shed further light on an area of nystagmus which has a large impact on those with the condition, i.e. the effect of stress on visual function, and that it will guide and inspire others to conduct more research in this area.

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Appendices

Appendix I: Subject information for those with nystagmus

ID	Sex/Age	Associations	Ocular Alignment	Null Position	Rx	VA (logMAR)	Rx Worn	Waveform	Investigation participated in
JaSh	M/40	Idiopathic	Ortho		R: PLANO	0.80	No	DJ	Orientation
					L: PLANO	0.80			
RB	M/23	Idiopathic	Ortho	10°	R: PLANO	0.10	No	JR_{EF}/JL_{EF}	Stress/Orientation
					L: -0.50DS	0.10			
JS	M/53	Idiopathic	Ortho	12°	R: -12.00/-2.00 x 32	0.30	Yes	JL_{EF}	Stress/Orientation
					L: -10.50/-1.00 x 90	0.30			
RW	M/30	Ocular Albinism	Ortho	Primary	R: PLANO	0.56	No	AP/PP_{FS}	Stress
					L: PLANO	0.46			
RC	M/38	Ocular Albinism	R ET	5°	R: +4.25/-4.50 x 6	0.48	Yes	DJ/PC	Stress/Orientation
					L: +5.25/-5.00 x 165	0.26			
VO	F/28	Idiopathic	Ortho	Primary	R: -1.00DS	0.00	No	PP_{FS}	Stress
					L: -0.25DS	0.00			
WL	F/48	Idiopathic	Exop	-5°	R: -1.50DS	0.40	Yes	PP_{FS}	Stress
					L: -1.50DS	0.40			
LL	M/53	Idiopathic	Esop	Primary	R: -0.25/-0.25 x 155	0.32	No	JL_{EF}/P_{FS}	Stress
					L: -0.50/-0.75 x 110	0.32			
JeSt	F/27	Idiopathic	Ortho	Primary	R: -1.50/-1.75 x 5	0.00	Yes	JR_{EF}	Stress
					L: -1.00/-1.75 x 175	0.08			
MH	M/47	Idiopathic	R Hyperp	10°	R: +4.50/-1.00 x 165	0.38	Yes	PP_{FS}/DJ	Stress/Orientation
					L: +3.25/-1.00 x 180	0.36			
GTh	M/58	Idiopathic	R ET		R: -3.50/-1.75 x 135	0.82	Yes	P	Orientation
					L: -4.75/-2.00 x 160	0.82			
JqA	F/46	Idiopathic	Ortho	5°	R: +5.50/-5.00 x 10	0.26	Yes	P_{FS}	Stress/Orientation
					L: +4.00/-5.00 x 180	0.30			
GT	M/60	Idiopathic	Ortho	Primary	R: -2.00/-0.50 x 25	0.52	Yes	P_{FS}	Stress/Orientation
					L: -0.75/-0.50 x 130	0.40			

Appendix I: Subject information for those with nystagmus

CT	F/54	Idiopathic	R XT	15°	R: -5.50DS	0.28	Yes	P/DJ	Stress/Orientation
					L: -5.50DS	0.14			
KL	F/58	Idiopathic	L XT (corrected)	Primary	R: -0.75/-0.50 x 165	0.00	Yes	DJ	Stress/Orientation
					L: +0.25/-0.25 x 180	0.12			
JM	M/41	Ocular Albinism	L ET	Primary	R: +7.75/-2.75 x 160	0.56	Yes	PC	Stress/Orientation
					L: +7.50/-2.75 x 60	0.92			
CM	F/59	Idiopathic	L ET	-15°	R: PLANO	0.50	No	PP_{FS}	Stress/Orientation
					L: PLANO	0.60			
MB	F/57	Idiopathic	L XT	Primary	R: -0.25/-1.50 x 10	0.50	Yes	DJ	Stress/Orientation
					L: +2.75/-2.00 x 17	0.60			
MT	F/67	Idiopathic	Ortho	Primary	R: +4.25/-0.75 x 30	0.60	Yes	JL_{EF}	Stress/Orientation
					L: +5.50/-1.25 x 180	0.78			
VW	F/20	Idiopathic	Alt ET	-5°	R: +2.25/-3.75 x 19	0.32	Yes	JR_{EF}	Stress/Orientation
					L: +2.50/-3.75 x 161	0.34			
SW	F/67	Idiopathic	Ortho	5°	R: PLANO	0.40	No	DJ	Stress/Orientation
					L: PLANO/-0.50 x 180	0.40			
LC	M/26	Idiopathic	L ET	Primary	R: +3.75/-2.75 x 165	0.56	Yes	PP_{FS}	Stress/Orientation
					L: +3.75/-3.25 x 35	0.70			
RN	M/71	Albinism	R ET	Primary	R: +1.75/-2.00 x 180	0.84	Yes	DJ	Stress/Orientation
					L: +2.50/-2.00 x 180	0.60			
ML	M/31	Ocular Albinism	Alt ET		R: +7.00DS	0.70	Yes	P	Orientation
					L: +7.00DS	0.80			
JT	M/22	Idiopathic	Ortho		R: -2.50/-1.00 x 170	0.64	Yes	JL_{EF}	Orientation
					L: -2.00/-1.25 x 175	0.68			
DW	F/29	Idiopathic	Ortho	Primary	R: -5.00DS	0.00	Yes	JR_{EF}	Stress/Orientation
					L: -5.00DS	0.00			
CW	F/19	Idiopathic	Ortho	Primary	R: PLANO /-0.50 x 180	0.40	No	P	Stress
					L: PLANO/-0.50 x 180	0.40			

Appendix I: Subject information for those with nystagmus

FH	F/28	Idiopathic	Ortho	INTERVIEW ONLY
MVDH	F/30	Ocular Albinism	Ortho	INTERVIEW ONLY

Table 1: Clinical information for subjects with nystagmus. Ortho - Orthophoric, Alt - Alternating, ET - Esotropia, XT - Exotropia, L - Left, R - Right, Hyperp - Hyperphoria. Positive values of null position indicate a rightward gaze direction, negative indicate a leftward gaze direction, Primary - null position in primary gaze (i.e. 0°). Stress - Effect of stress on visual function investigation (chapter 6), Orientation - Effect of stimulus orientation on VA investigation (chapter 4). DJ - Dual Jerk, JR - Jerk Right, JL - Jerk Left, AP - Asymmetric Pendular, PP - Pseudo-pendular, PC - Pseudo-cycloid, P - Pendular, EF - Extended foveation, FS - Foveating saccades

Appendix II: Subject information for controls

ID	Sex/Age	Ocular Alignment	Rx	VA (logMAR)	Rx Worn	Investigation participated in
CP	F/41	Ortho	R: -3.50/-1.00 x 5	0.00	Yes	Stress/Orientation
			L: -2.75/-0.50 x 160	0.00		
JW	M/58	Ortho	R: +0.50/-0.50 x 90	0.00	Yes	Stress/Orientation
			L: +2.50/-0.50 x 95	0.00		
BP	F/29	Ortho	R: -1.25DS	-0.10	Yes	Orientation
			L: -1.00DS	-0.10		
MW	F/62	Ortho	R: -2.50/-1.00 x 180	-0.06	Yes	Orientation
			L: -2.50/-1.75 x 140	-0.06		
SC	F/21	Ortho	R: -0.50/-0.25 x 180	-0.10	No	Stress/Orientation
			L: -0.50/-0.25 x 180	-0.10		
POJ	M/61	Ortho	R: +2.25/-0.50 x 40	0.00	Yes	Stress/Orientation
			L: +2.25/-0.25 x 100	0.00		
PAJ	F/61	Exop	R: +1.50/-0.50 x 30	0.10	Yes	Stress/Orientation
			L: +1.75/-0.75 x 180	0.00		
HJ	F/29	Ortho	R: -2.00/-0.75 x 168	-0.10	Yes	Stress/Orientation
			L: -1.25/-0.75 x 12	-0.10		
EM	F/26	Ortho	R: -8.00/-1.00 x 180	0.10	Yes	Orientation
			L: -8.00/-1.00 x 180	0.10		
MA	M/27	Ortho	R: +0.75DS	-0.06	No	Stress/Orientation
			L: +0.75DS	-0.10		
MS	F/30	Ortho	R: PLANO/-0.25 x 180	-0.10	No	Orientation
			L: PLANO	-0.10		
GF	M/27	Ortho	R: -1.75/-0.25 x 80	-0.10	Yes	Stress
			L: -2.50/-0.25 x 88	-0.10		
CB	M/26	Ortho	R: -1.25/-0.50 x 180	-0.02	Yes	Stress
			L: -1.00DS	-0.02		
JD	F/26	Esop	R: PLANO/-0.75 x 90	0.00	No	Stress
			L: -0.25/-0.75 x 90	0.00		
LC	F/26	Ortho	R: +0.25DS	-0.10	No	Stress/Orientation
			L: +0.25DS	-0.10		
GE	M/31	Ortho	R: -0.75/-0.75 x 65	0.10	Yes	Stress
			L: -0.75/-0.75 x 95	-0.10		
CT	M/31	Ortho	R: PLANO	-0.10	No	Stress
			L: PLANO	-0.10		
SN	F/32	Ortho	R: -3.00DS	0.10	Yes	Stress/Orientation
			L: -2.00DS	0.10		
AM	M/33	Ortho	R: -2.75/-0.50 x 90	-0.10	Yes	Stress
			L: -3.50/-0.50 x 85	0.00		
TW	M/47	Ortho	R: +2.50/-0.25 x 80	0.00	Yes	Stress
			L: +3.50/-0.50 x 90	0.00		
SH	F/55	Ortho	R: PLANO	0.10	No	Orientation
			L: PLANO	0.10		
JS	M/36	Ortho	R: PLANO	0.00	No	Orientation
			L: +0.25DS	0.00		

DR	F/21	Ortho	R: -4.25DS	0.00	Yes	Orientation
			L: -2.75/-0.25 x 180	0.00		
CCH	F/21	Ortho	R: -1.75/-0.75 x 5	0.00	Yes	Orientation
			L: -3.25/-0.75 x 170	0.00		
CD	F/33	Ortho	R: PLANO	0.00	No	Orientation
			L: PLANO/-0.25 x 180	0.00		
AW	M/25	Ortho	R: -4.75/-0.75 x 170	-0.10	Yes	Orientation
			L: -5.50/-0.75 x 10	-0.10		
ED	F/28	Esop	R: -0.25DS	-0.20	No	Stress/Orientation
			L: -0.25DS	-0.20		
KE	F/32	Ortho	R: -3.00/-0.50 x 90	0.00	Yes	Stress
			L: -3.00/-0.25 x 180	-0.10		
MC	M/29	Ortho	R: PLANO	0.00	No	Stress
			L: PLANO	0.00		
SM	F/25	Ortho	R: PLANO	0.00	No	Stress
			L: PLANO	0.00		
PJ	M/28	Exop	R: +0.25/-0.25 x 155	-0.10	No	Orientation
			L: +0.75/-0.50 x 170	-0.10		

Table 2: Clinical information for control subjects. Ortho - Orthophoric, Alt - Alternating, ET - Esotropia, XT - Exotropia, Exop - Exophoria, Esop - Esophoria, L - Left, R - Right, Hyperp - Hyperphoria. Stress - Effect of stress on visual function investigation (chapter 6), Orientation - Effect of stimulus orientation on VA investigation (chapter 4)

Patient Information Leaflet

Study Title:

The Effects of Stimulus Orientation on the Visual Acuity of People with Congenital Nystagmus

What is the purpose of this study?

Congenital Nystagmus is an involuntary movement of the eyes. It presents at birth or early in the child's visual development. Nystagmus, in the majority of cases, causes a reduction in the person's vision.

The number of people quoted to suffer with Nystagmus varies. However, the Nystagmus Network puts this number at be 1 in 1000 adults, and 1 in 640 children.

Due to the fact that most nystagmus waveforms show a movement in the horizontal direction, there is much debate in the literature about whether people with nystagmus see vertical or horizontal oriented targets better.

The aim of this study is to measure the differences in the vision of people with nystagmus when looking at different targets with either vertical or horizontal orientations.

Why have I been chosen?

We are aiming to recruit 25 subjects with congenital nystagmus.

Who is organizing the study?

The study is organized by the Research Unit for Nystagmus (RUN) at the School of Optometry and Vision Sciences, Cardiff University. The study is funded by the College of Optometrists.

What will happen during the experiment?

Each participant will attend the School of Optometry and Vision Sciences building (Maindy Road) for one session, lasting no more than 90 minutes.

Vision will be recorded by looking at three types of visual stimuli (a letter C, a letter E, and a grating). During the investigation, you will be asked to tell us whether the letters are positioned to the left or right (horizontally), and then whether you think they are positioned up or down (vertically). As the tests go on, the stimuli will become increasingly more difficult to see. The test will be carried out three times for each stimulus. Your eye movements will not be recorded during this investigation, unless you have not taken part in any of our investigations before. In which case, a brief recording will be made. The recording equipment consists of small infrared lights attached to a head band worn on your head. Nothing will touch your eyes during the experiment.

What are the possible benefits of taking part?

Although no immediate benefit is likely to arise as a result of this study, we hope that the information obtained will contribute to the long-term understanding of nystagmus, and therefore aid the future development of therapeutic and/or rehabilitative techniques designed to maximize the visual potential of people with nystagmus.

Are there any disadvantages to taking part in this study?

No. If you feel uncomfortable at any point during the study, the experiment can be stopped and no further participation is necessary.

Confidentiality, who will know I am taking part in this study?

All information that is collected about you during the course of the research will be kept strictly confidential. Any information about you will be encoded so that you cannot be recognized from it.

Travelling Expenses

We will pay your travelling expenses.

Ethics

This study has been approved by the School of Optometry and Vision Sciences Ethics Committee.

What will happen to the results of this study?

We aim to publish the results of this research in scientific journals. If you are interested, we can also summarise the results in an information sheet for you.

Contact for further information

Please feel free to ask further questions by contacting:

Mr Philip Jones on (029) 20870580, E-Mail JonesPH@cardiff.ac.uk

Or

Dr. Jon Erichsen on (029) 20875656, E-Mail ErichsenJT@cardiff.ac.uk

Many thanks,

Phil Jones

The Effects of Stimulus Orientation on the Visual Acuity of People with Congenital Nystagmus

Researchers: Philip Jones, Dr Jon Erichsen

Consent Form

Please tick

- I have read and understood the Information sheet and have been given the opportunity to ask questions. ☐
- I understand that my participation is voluntary and that I am free to withdraw at any time. ☐
- I agree to take part in the study. ☐
- I would like to receive information on the results of this investigation ☐

Name

(Printed):.....

Signed:.....

Date:.....

Subject Information Leaflet

Study Title:

The effects of the position of TENS electrodes on GSR response

What is the purpose of this study?

In vision research it is necessary to be able to maintain the subject's fixation on the visual task at all times. When looking for a prolonged stressor for investigations it becomes apparent that many well known systems require looking at pictures etc which disrupts fixation.

The Transcutaneous Electrical Nerve Stimulation (TENS) machine is a commercially available instrument used for pain relief. It works by interrupting neural signals from the area where the electrodes are placed by using small electrical impulses. These impulses do not reach dangerous levels. The TENS, when set at a subject's threshold can create a mild feeling of stress. As with most things, this feeling is variable depending on the person. It is for this reason that we are looking at the TENS machine as a possible experimental stressor. The amount of stress caused by a stressor is measured using Galvanic Skin Response (GSR). This measures the electrical resistance of the skin. These readings show changes during emotional stimulation and/or arousal.

However the GSR is also affected by the movement of the body and a secondary effect of the TENS is that it can cause contraction of the muscles in the area where the electrodes are placed. Because of this readings could be abnormally affected by the use of a TENS machine during muscle contraction if the electrodes are placed inappropriately.

The aim of this study is to measure the GSR response when the TENS machine electrodes are placed on the opposite arm to that with the GSR electrodes attached, in order to show that the TENS machine can be used as an experimental stressor with minimum artefacts on the GSR recording.

Why have I been chosen?

We are recruiting 30 people to take part in the study. Subjects must be 18 or over. Subjects should not take part if the may be pregnant, suffer with leprosy, chronic alcoholism, skin disease, heart conditions or have a pacemaker fitted.

Who is organizing this study?

The study is organized by the Research Unit for Nystagmus (R.U.N.) at the School of Optometry and Vision Sciences, Cardiff University.

What will happen during the experiment?

Each participant will attend the School of Optometry and Institute of Vision (Maindy Road) for one or two sessions each lasting no longer than 40 minutes.

Your level of stress will be recorded using the GSR for a period of approximately 30 minutes. The TENS machine will be placed on the opposite arm to that with the GSR. There will be an initial period of relaxation, followed by the assessment of the subjects threshold on the TENS machine. There will then be a period of relaxation again, this time followed by a period where the TENS machine may be switched on at any time. The final part will entail a further period of relaxation.

What are the possible benefits of taking part?

Although there are no immediate benefits likely from this study, we hope that the information obtained will aid us in developing a clinical stressor. This will allow us to perform further studies into the visual function of people with nystagmus.

Are there any disadvantages to taking part?

No, if you feel anxious or uncomfortable at any point during the study, the experiment can be stopped and no further participation is necessary.

Confidentiality – Who will know I am taking part in the study?

All information that is collected about you during the course of the research will be kept strictly confidential. Any information about you will be encoded so that you cannot be recognised from it.

Ethics

This study has been approved by the School of Optometry Ethical Committee.

What will happen to the results of this study?

The results of this study will help us to develop an experimental stressor in order to advance our research into visual function in Nystagmus. If you are interested, we can also summarise the results in an information sheet for you.

Contact for further information

Please feel free to ask further questions by contacting:

Mr Philip Jones on 02920870580, E-Mail: JonesPH@cardiff.ac.uk

Or

Dr Jon Erichsen on 02920875656, E-Mail: ErichsenJT@cardiff.ac.uk

Many Thanks

Phil Jones

Positioning of TENS electrodes and its effects on GSR recordings

Researchers: Philip Jones, Dr Jon Erichsen

Consent Form

Please tick

- I have read and understood the Information sheet and have been given the opportunity to ask questions. ☐
- I understand that my participation is voluntary and that I am free to withdraw at any time. ☐
- I agree to take part in the study. ☐
- I would like to receive information on the results of this investigation ☐

Name

(Printed):.....

Signed:.....

Date:.....

Patient Information Leaflet

Study Title:

The Impact of Stress on the Visual Function of people with Congenital Nystagmus

What is the purpose of this study?

Congenital Nystagmus is an involuntary movement of the eyes. It presents at birth or early in the child's visual development. Nystagmus, in the majority of cases, causes a reduction in the person's vision.

The number of people quoted to suffer with Nystagmus varies. However, the Nystagmus Network puts this number at be 1 in 1000 adults, and 1 in 640 children.

In recent years our understanding of nystagmus has been greatly improved with the aid of eye movement recordings. There is a commonly held belief that effort-to-see worsens nystagmus. A recent study from our research unit has shown that making an effort to see does not worsen nystagmus as long as there is no stress involved. We have therefore identified stress as an important factor in nystagmus. It is often quoted of people with nystagmus that their vision and nystagmus get worse when they are under stress; however, this has

not been measured in the past.

The aim of this study is to quantitatively measure the changes in intensity of nystagmus and its effect on vision during periods of stress.

Why have I been chosen?

We are aiming to recruit 25 subjects with congenital nystagmus. All subjects should have no recent history of migraine, or light sensitive epilepsy. Subjects should not take part if they may be pregnant, suffer with leprosy, chronic alcoholism, skin disease, heart conditions or have a pacemaker fitted.

Who is organizing the study?

The study is organized by the Research Unit for Nystagmus (RUN) at the School of Optometry and Vision Sciences, Cardiff University. The study is funded by the College of Optometrists.

What will happen during the experiment?

Each participant will attend the School of Optometry and Vision Sciences building (Maindy Road) for one or two sessions, each lasting no more than 90 minutes.

Your eye movements will be recorded while you view targets which will become increasingly difficult to see. The recording equipment consists of small infrared lights attached to a head band worn over your head. Nothing will

touch your eyes during the experiment.

In order to induce a state of stress we will be using a Transcutaneous Electrical Nerve Stimulation (TENS) machine. This will involve two electrode pads being placed on one of your arms. The TENS machine is a commercially available instrument which is usually used for pain relief, and works by interrupting nervous signals from the area in which the pads are placed with electrical impulses. These impulses do not reach harmful levels.

Your eye movements and level of vision will be measured four times during the experiment, twice with the TENS machine on, and twice without the TENS machine.

What are the possible benefits of taking part?

Although no immediate benefit is likely to arise as a result of this study, we hope that the information obtained will contribute to the long-term understanding of nystagmus, and therefore aid the future development of therapeutic and/or rehabilitative techniques designed to maximize the visual potential of people with nystagmus.

Are there any disadvantages to taking part in this study?

No. If you feel uncomfortable at any point during the study, the experiment can be stopped and no further participation is necessary.

Confidentiality, who will know I am taking part in this study?

All information that is collected about you during the course of the research will be kept strictly confidential. Any information about you will be encoded so that you cannot be recognized from it.

Travelling Expenses

We will pay your travelling expenses.

Ethics

This study has been approved by the School of Optometry and Vision Sciences Ethics committee.

What will happen to the results of this study?

We aim to publish the results of this research in scientific journals. If you are interested, we can also summarise the results in an information sheet for you.

Contact for further information

Please feel free to ask further questions by contacting:

Mr Philip Jones on 02920870580, E-Mail JonesPH@cardiff.ac.uk

Or

Dr. Jon Erichsen on 02920875656, E-Mail ErichsenJT@cardiff.ac.uk

Many Thanks

Phil Jones

The Impact of Stress on the Visual Function of people with Congenital Nystagmus

Researchers: Philip Jones, Dr Jon Erichsen

Consent Form

Please tick

- I have read and understood the Information sheet and have been given the opportunity to ask questions. ☐
- I understand that my participation is voluntary and that I am free to withdraw at any time. ☐
- I agree to take part in the study. ☐
- I would like to receive information on the results of this investigation ☐

Name

(Printed):.....

Signed:.....

Date:.....

Patient Information Leaflet

Study Title:

The Perception of the Impact of Stress on those with Nystagmus

What is the purpose of this study?

Congenital Nystagmus is an involuntary movement of the eyes. It presents at birth or early in the child's visual development. Nystagmus, in the majority of cases, causes a reduction in the person's vision. The number of people quoted to suffer with Nystagmus varies. However, the Nystagmus Network puts this number at 1 in 1000 adults, and 1 in 640 children.

In recent years our understanding of nystagmus has been greatly improved with the aid of eye movement recordings but there is much still to learn. It is often quoted by people with nystagmus that their vision and nystagmus get worse when they are under stress; however, this statement is very broad in its meaning.

The aim of this study is to better understand what people with nystagmus experience when stressed.

Why have I been chosen?

This questionnaire is being sent to members of the nystagmus network.

Who is organizing the study?

The study is organized by the Research Unit for Nystagmus (RUN) at the School of Optometry and Vision Sciences, Cardiff University. The study is funded by the College of Optometrists.

What am I expected to do?

All we require is that you complete the attached questionnaire and return it to us in the stamped addressed envelope provided. You are under no obligation to complete and return this questionnaire.

What are the possible benefits of taking part?

Although no immediate benefit is likely to arise as a result of this study, we hope that the information obtained will contribute to our long-term understanding of nystagmus, and therefore aid the future development of therapeutic and/or rehabilitative techniques designed to maximize the visual potential of people with nystagmus.

Are there any disadvantages to taking part in this study?

No. You are under no obligation to complete and return this questionnaire.

Confidentiality, who will know I am taking part in this study?

All information that is collected about you during the course of the research will be kept strictly confidential. Any information about you will be encoded so that you cannot be recognized from it.

Ethics

This study has been approved by the School of Optometry Ethics committee.

What will happen to the results of this study?

We aim to publish the results of this research in scientific journals. If you are interested, we can also summarise the results in an information sheet for you.

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Many Thanks

Phil Jones

The Perception of the Impact of Stress on those with Nystagmus

Researchers: Philip Jones, Dr Jon Erichsen

Consent Form

Please tick

- I have read and understood the Information sheet and have been given the opportunity to ask questions. ☐
- I understand that my participation is voluntary and that I am free to withdraw at any time. ☐
- I agree to take part in the study. ☐
- I would like to receive information on the results of this investigation ☐

Name

(Printed):.....

Signed:.....

Date:.....

Appendix IV: Raw data for the investigation into the effects of stimulus orientation on VA

ID	Age/Sex	Diagnosis	VA	VA Tumbling E		VA Landolt C		VA Gratings		Differences		
				H	V	H	V	H	V	Tumb E	Land C	Gratings
Nystagmus												
JT	22/M	Idiopathic	0.64	0.40	0.46	0.41	0.34	0.64	0.62	0.06	-0.07	-0.02
CT	54/F	Idiopathic	0.14	0.17	0.19	0.07	0.21	0.38	0.55	0.02	0.14	0.17
JM	41/M	Ocular Albinism	0.56	0.50	0.36	0.45	0.46	0.62	0.66	-0.14	0.01	0.04
RC	38/M	Ocular Albinism	0.26	0.38	0.22	0.21	0.14	0.39	0.47	-0.16	-0.07	0.08
JS	53/M	Idiopathic	0.46	0.19	0.19	0.21	0.26	0.48	0.48	0	0.05	0
MH	47/M	Idiopathic	0.36	0.15	0.11	0.15	0.12	0.35	0.46	-0.04	-0.03	0.11
JA	46/F	Idiopathic	0.26	0.20	0.21	0.13	0.23	0.39	0.58	0.01	0.1	0.19
ML	31/M	Ocular Albinism	0.70	0.56	0.43	0.46	0.47	0.66	0.84	-0.13	0.01	0.18
GT	58/M	Idiopathic	0.82	0.97	0.87	0.95	0.92	0.98	1.01	-0.1	-0.03	0.03
KL	58/F	Idiopathic	0.00	-0.14	-0.18	-0.22	-0.16	0.14	0.12	-0.04	0.06	-0.02
GTe	60/M	Idiopathic	0.40	0.24	0.38	0.24	0.26	0.47	0.49	0.14	0.02	0.02
DW	29/F	Idiopathic	0.00	-0.16	-0.10	-0.26	-0.01	0.13	0.21	0.06	0.25	0.08
RN	71/M	Albinism	0.60	0.52	0.34	0.40	0.34	0.62	0.64	-0.18	-0.06	0.02
LC	26/M	Idiopathic	0.56	0.32	0.31	0.24	0.43	0.54	0.60	-0.01	0.19	0.06
SW	67/F	Idiopathic	0.40	0.18	0.26	0.23	0.18	0.49	0.53	0.08	-0.05	0.04
RB	23/M	Idiopathic	0.10	-0.11	-0.23	-0.21	-0.19	0.11	0.11	-0.12	0.02	0
VW	20/F	Idiopathic	0.32	0.25	0.50	0.24	0.23	0.54	0.47	0.25	-0.01	-0.07
CM	59/F	Idiopathic	0.50	0.12	0.18	0.09	0.13	0.47	0.38	0.06	0.04	-0.09
MT	67/F	Idiopathic	0.60	0.37	0.40	0.55	0.41	0.63	0.67	0.03	-0.14	0.04
MB	57/F	Idiopathic	0.50	0.08	0.08	0.05	0.15	0.30	0.27	0	0.1	-0.03
JaSh	40/M	Idiopathic	0.80	0.59	0.60	0.59	0.90	0.57	0.59	0.01	0.31	0.02

Table 1: Raw data for all subjects with nystagmus showing VA measured with each stimulus and orientation

Appendix IV: Raw data for the investigation into the effects of stimulus orientation on VA

ID	Age/Sex	VA	VA Tumbling E		VA Landolt C		VA Gratings		Differences		
			H	V	H	V	H	V	Tumb E	Land C	Gratings
Controls											
BP	29/F	-0.10	-0.23	-0.27	-0.43	-0.26	-0.03	0.07	-0.04	0.17	0.10
HM	30/F	-0.10	-0.24	-0.14	-0.35	-0.34	-0.11	-0.06	0.10	0.01	0.05
MW	62/F	-0.06	-0.32	-0.23	-0.27	-0.26	0.04	0.04	0.09	0.01	0.00
EM	26/F	0.10	-0.15	-0.13	-0.26	-0.20	0.13	0.27	0.02	0.06	0.14
MA	27/M	-0.10	-0.35	-0.32	-0.42	-0.42	-0.02	-0.05	0.03	0.00	-0.03
HJ	29/F	-0.10	-0.27	-0.18	-0.27	-0.29	0.03	0.04	0.09	-0.02	0.01
AW	25/M	-0.10	-0.32	-0.24	-0.32	-0.32	-0.10	-0.03	0.08	0.00	0.07
PJ	28/M	0.00	-0.26	-0.23	-0.35	-0.31	-0.01	-0.02	0.03	0.04	-0.01
SH	55/F	0.10	-0.16	-0.13	-0.23	-0.21	0.06	0.08	0.03	0.02	0.02
SN	32/F	0.10	-0.24	-0.19	-0.20	-0.14	0.09	0.07	0.05	0.06	-0.02
CCH	21/F	0.00	-0.04	0.06	-0.04	-0.06	0.25	0.19	0.10	-0.02	-0.06
SC	21/F	-0.10	-0.23	-0.19	-0.26	-0.32	0.02	0.04	0.04	-0.06	0.02
DR	21/F	0.00	-0.19	-0.15	-0.23	-0.21	0.18	0.14	0.04	0.02	-0.04
CD	33/F	0.00	-0.26	-0.13	-0.29	-0.23	0.07	0.03	0.13	0.06	-0.04
LC	26/F	-0.10	-0.26	-0.22	-0.34	-0.34	-0.06	-0.06	0.04	0.00	0.00
POJ	62/M	0.00	-0.24	-0.13	-0.26	-0.22	0.05	0.08	0.11	0.04	0.03
PAJ	61/F	0.10	-0.23	-0.08	-0.20	-0.21	0.17	0.08	0.15	-0.01	-0.09
JS	36/M	0.00	0.11	0.08	0.13	0.00	0.23	0.20	-0.03	-0.13	-0.03
JW	58/M	0.00	-0.26	-0.13	-0.29	-0.20	0.09	0.08	0.13	0.09	-0.01
CP	42/F	0.00	-0.18	-0.11	-0.29	-0.29	0.10	0.07	0.07	0.00	-0.03

Table 2: Raw data for all control subjects showing VA measured with each stimulus and orientation

Appendix V: Raw data for the investigation into the effects of stress on visual function in those with nystagmus

ID	Age/Sex	VA				Amplitude				Frequency				Intensity			
		R1	TD	AA	R2	R1	TD	AA	R2	R1	TD	AA	R2	R1	TD	AA	R2
CM	59/F	0.40	0.42	0.41	0.45	5.98	4.37	4.23	3.20	4.50	3.83	3.83	4.50	26.91	16.75	16.23	14.41
SW	67/F	0.26	0.24	0.26	0.28	0.65	0.57	0.39	0.81	3.17	3.67	3.50	3.50	2.07	2.08	1.36	2.83
LC	26/M	0.53	0.48	0.39	0.29	1.09	0.61	0.34	0.52	5.30	5.00	4.00	4.33	5.80	3.07	1.36	2.26
RB	23/M	0.17	0.03	0.04	0.30	6.32	2.29	4.01	1.79	4.33	5.33	4.33	5.33	27.39	12.2	17.37	9.53
KL	58/F	0.05	0.21	0.12	0.10	0.31	0.34	0.62	0.64	2.00	2.83	2.50	1.83	0.63	0.97	1.56	1.18
JqA	46/F	0.57	0.50	0.56	0.57	1.10	0.72	1.15	1.33	6.33	6.67	7.33	6.67	6.94	4.83	8.43	8.87
JeSt	27/F	0.28	0.19	0.15	0.17	3.03	3.78	2.98	2.52	5.67	5.17	4.83	5.00	17.19	19.55	14.39	12.6
MH	47/M	0.43	0.54	0.60	0.42	1.69	3.48	1.70	0.95	4.67	4.67	3.50	2.33	7.90	16.23	5.96	2.22
CT	54/F	0.31	0.40	0.39	0.33	0.65	1.68	0.83	1.00	1.80	1.80	2.20	1.50	1.17	3.02	1.82	1.49
DW	29/F	0.06	-0.02	0.06	0.11	4.02	4.38	1.57	2.08	4.00	4.80	4.50	4.50	16.06	21.01	7.04	9.34
GT	60/M	0.38	0.39	0.38	0.37	3.25	4.32	0.84	1.33	4.30	4.20	4.80	4.20	13.99	18.14	4.02	5.58
JS	53/M	0.47	0.70	0.71	0.68	0.65	8.17	7.83	4.34	3.70	4.80	5.20	4.80	2.40	39.22	40.73	20.85
LL	53/M	0.39	0.35	0.23	0.32	1.67	1.95	1.55	0.90	3.50	3.50	3.80	3.50	5.83	6.84	5.90	3.13
VO	28/F	0.11	0.09	0.14	0.13	1.57	2.06	2.10	1.98	3.50	3.80	3.50	3.00	5.49	7.83	7.37	5.95
MB	57/F	0.38	0.25	0.28	0.25	1.48	0.45	0.50	0.49	2.00	1.33	1.17	2.00	2.95	0.60	0.59	0.98
MT	67/F	0.50	0.53	0.42	0.46	0.71	0.91	0.96	0.66	4.17	3.67	4.17	4.00	2.94	3.34	3.98	2.64
JM	41/M	0.62	0.54	0.51	0.56	2.00	2.27	1.37	1.25	4.67	4.17	3.67	3.33	9.34	9.46	5.04	4.17
RC	38/M	0.46	0.40	0.42	0.38	0.23	0.67	0.34	0.25	3.30	3.20	2.70	2.50	0.74	2.14	0.93	0.63
RW	30/M	0.60	0.57	0.60	0.62	3.94	3.37	3.62	2.48	2.67	6.67	5.83	5.17	10.51	22.46	21.09	12.81
WL	48/F	0.35	0.27	0.27	0.28	2.85	2.27	3.01	2.43	3.70	3.70	3.70	3.30	10.55	8.39	11.15	8.00
VW	20/F	0.62	0.37	0.52	0.47	2.42	2.57	3.29	4.82	3.83	3.00	3.50	4.00	9.27	7.71	11.51	19.27
RN	71/M	0.55	0.50	0.44	0.49	1.40	2.53	2.13	1.38	1.33	1.67	2.17	2.17	1.87	4.21	4.61	2.99
CW	19/F	0.30	0.36	0.21	0.34	1.80	2.62	0.97	0.47	2.83	2.17	1.50	2.00	5.09	5.67	1.46	0.95

Table 1: Raw data of VA, amplitude, frequency, and intensity for subjects with nystagmus. R1 - First relaxed period, TD - Task demand period, AA - Anticipatory anxiety period, R2 - Second relaxed period

Appendix V: Raw data for the investigation into the effects of stress on visual function in those with nystagmus

ID	Age/Sex	Corrected SkC				Response Time				Foveation Duration (ms)				SD			
		R1	TD	AA	R2	R1	TD	AA	R2	R1	TD	AA	R2	R1	TD	AA	R2
CM	59/F	-1.48	2.35	0.21	0.06	1.12	1.08	1.53	1.02	5.78	22.44	30.74	19.11	0.0094	0.0094	0.0095	0.0086
SW	67/F	-1.12	0.63	0.91	1.04	4.25	6.13	2.86	1.65	210.47	145.41	205.86	133.86	0.0110	0.0114	0.0300	0.0182
LC	26/M	-5.79	3.02	3.87	2.84	1.14	1.25	1.07	1.12	69.78	101.33	201.08	163.73	0.0246	0.0461	0.0503	0.0533
RB	23/M	-0.69	1.74	0.34	-0.11	0.66	1.59	0.79	0.57	52.69	41.63	61.19	52.69	0.0272	0.0169	0.0407	0.0095
KL	58/F	0.43	1.07	0.07	-2.11	3.03	0.98	1.29	1.21	450.08	285.12	319.40	463.36	0.0460	0.0444	0.0869	0.0547
JqA	46/F	1.75	0.00	-1.48	-1.3	0.80	0.68	0.73	0.65	37.00	42.43	28.39	23.20	0.0123	0.0134	0.0123	0.0103
JeSt	27/F	-2.76	2.72	2.09	0.32	3.43	2.15	1.14	1.03	22.85	24.84	31.28	36.43	0.0098	0.0102	0.0147	0.0106
MH	47/M	-0.25	2.2	-0.48	-4.45	1.71	2.34	1.24	1.25	54.82	20.00	80.48	266.50	0.0154	0.0125	0.0126	0.0244
CT	54/F	-0.06	1.65	1.91	-2.86	1.88	1.26	1.64	1.49	360.46	270.71	268.23	373.10	0.0234	0.0231	0.0146	0.0157
DW	29/F	-0.14	0.32	0.63	0.14	1.37	1.97	0.70	0.83	97.46	51.19	111.85	78.41	0.0299	0.0216	0.0314	0.0246
GT	60/M	-1.16	1.42	1.08	0.1	4.24	2.24	1.20	1.30	3.65	11.48	57.20	38.44	0.0193	0.0058	0.0096	0.0088
JS	53/M	-	-	-	-	1.65	3.43	1.83	1.49	156.55	1.31	1.97	2.03	0.0341	0.0051	0.0050	0.0039
LL	53/M	0.29	-0.19	-0.71	-0.75	1.68	4.21	2.82	2.13	96.33	81.76	89.00	143.24	0.0124	0.0153	0.0125	0.0229
VO	28/F	-1.32	1.47	0.49	0.46	1.50	1.61	0.97	0.86	50.19	25.35	42.10	45.56	0.0094	0.0069	0.0100	0.0089
MB	57/F	-0.22	0.69	0.08	-1.09	1.52	1.04	0.83	1.21	214.58	691.50	730.71	426.92	0.0131	0.0498	0.0415	0.0235
MT	67/F	0.33	0.99	-0.28	-0.73	2.49	1.62	2.07	1.09	94.64	102.59	91.08	120.21	0.0228	0.0243	0.0145	0.0174
JM	41/M	0.71	2.11	0.54	0.34	2.13	2.19	1.56	1.60	35.61	38.64	94.68	108.80	0.0186	0.0190	0.0445	0.0411
RC	38/M	-	-	-	-	1.42	1.17	1.19	1.24	229.20	195.53	289.88	370.67	0.0336	0.0446	0.0427	0.0580
RW	30/M	0.47	0.07	0.31	0.58	1.87	1.61	1.00	0.88	21.69	11.40	10.03	11.42	0.0090	0.0091	0.0090	0.0051
WL	48/F	1.02	1.62	-2.58	-0.49	1.99	1.98	1.75	1.74	30.91	26.32	22.96	34.80	0.0111	0.0094	0.0096	0.0099
VW	20/F	-1.44	1.28	1.93	0.66	1.15	1.27	0.83	0.90	58.61	102.39	54.19	21.88	0.0120	0.0145	0.0146	0.0117
RN	71/M	-0.68	0.50	0.29	0.62	1.80	1.00	1.41	1.64	292.00	193.60	149.62	247.00	0.0121	0.0152	0.0113	0.0228
CW	19/F	-	-	-	-	0.83	0.90	0.78	0.76	78.47	130.92	335.00	393.50	0.0090	0.0103	0.0135	0.0367

Table 2: Raw data of corrected SkC, response time, percentage foveation, and SD for subjects with nystagmus. R1 - First relaxed period, TD - Task demand period, AA - Anticipatory anxiety period, R2 - Second relaxed period, SkC - Skin conductance, SD - Standard deviation of eye position

Appendix V: Raw data for the investigation into the effects of stress on visual function in those with nystagmus

ID	Age/Sex	VA				Corrected SkC				Response Time			
		R1	TD	AA	R2	R1	TD	AA	R2	R1	TD	AA	R2
Cto	31/M	-0.11	-0.09	-0.10	0.10	-0.35	1.38	0.45	-1.45	1.57	1.55	1.34	0.88
GE	31/M	0.49	0.36	0.26	0.42	-	-	-	-	1.40	1.53	1.20	0.76
KE	32/F	-0.02	-0.08	0.05	0.06	-0.10	1.06	1.88	0.02	0.88	0.86	0.69	0.84
MC	29/M	0.09	0.16	0.14	0.33	-1.16	2.86	4.68	-4.68	1.46	1.66	1.00	0.91
MA	27/M	-0.14	-0.24	-0.26	-0.10	-1.60	2.89	1.18	0.18	1.13	1.31	0.97	0.79
SN	32/F	-0.01	-0.02	0.00	0.05	-1.02	0.21	1.27	0.75	1.03	1.12	1.03	0.90
TW	47/M	0.31	-0.11	-0.08	-0.12	-	-	-	-	0.75	1.50	1.32	1.53
AM	33/M	-0.03	0.11	0.12	0.15	-0.61	0.51	-0.19	-0.65	1.21	0.65	0.52	0.61
POJ	61/M	-0.06	-0.13	-0.13	-0.16	-0.87	1.43	-0.31	-1.50	1.20	1.74	1.56	1.16
PAJ	60/F	0.08	-0.03	-0.05	-0.06	-2.93	1.94	2.15	0.62	0.90	2.02	1.16	0.91
HAJ	29/F	-0.04	-0.05	-0.04	-0.01	-2.59	0.76	1.66	0.15	1.13	1.12	0.88	0.78
CP	41/F	0.24	0.06	0.26	0.30	-1.32	1.83	0.02	-0.06	0.54	0.87	0.48	0.60
LC	26/F	-0.06	0.02	0.05	-0.07	-1.50	0.28	0.71	1.58	0.65	0.62	0.71	1.04
CB	26/M	-0.17	-0.12	-0.15	-0.17	-	-0.11	-0.33	-0.69	1.20	0.85	1.10	1.14
ED	28/F	0.08	0.31	0.15	0.17	-1.01	1.10	0.92	0.72	1.55	0.66	1.17	1.06
GF	27/M	-0.04	-0.16	-0.13	-0.14	-1.65	1.21	1.05	0.98	1.22	2.51	1.87	1.43
JD	26/F	0.04	0.17	0.16	0.20	-1.10	-0.04	0.71	1.41	2.21	1.58	1.24	1.40
JW	58/M	-0.03	-0.05	-0.04	-0.09	-2.01	0.44	0.23	0.99	1.45	1.16	1.22	1.09
SC	21/F	0.32	0.11	0.26	0.13	-2.49	1.54	1.60	0.99	0.94	1.52	0.63	0.61
SM	25/F	-0.05	-0.13	-0.14	-0.14	-	-0.31	-0.10	0.20	1.33	1.50	1.43	1.52

Table 3: Raw data of VA, corrected SkC and response time for control subjects. SkC - Skin conductance, R1 - First relaxed period, TD - Task demand period, AA - Anticipatory anxiety period, R2 - Second relaxed period

Appendix VIa: Interview Schedule and Questionnaire used to Investigate the Perception of the Effects of Stress on Nystagmus

Outline of interview

1

- Do you feel that you get stressed?
- When do you feel that you are stressed?
- What is it about that situation that makes you feel stressed?
- Does that situation make you feel stressed all the time?

Repeat the above for all situations mentioned

2

- How do you feel you are affected by situation x?
- Do you feel that any changes occur to you in situation x?
- Do you feel that your eyes are affected by situation x?
    - How do you feel your eyes are affected?
- Do you feel that the movements of your eyes are affected by situation x?
    - How do you feel the movements of your eyes are affected?
- Do you feel that your vision changes in situation x?
    - How do you feel your vision changes?
- Are there any particular things you find more difficult to see?
- Is there anything in particular that changes to make things more difficult?

    i.e. Vision more blurry
    Things not as defined as they were
    Things a little more misty
    Take longer to see things

** Repeat the above line of inquiry for each situation mentioned in 1**

Final Question

- Describe as best you can how you seen the world.

COMPLETE AND RETURN THIS QUESTIONNAIRE BEFORE THE END OF JANUARY 2010 AND BE ENTERED INTO A PRIZE DRAW TO WIN AN iPOD SHUFFLE MP3 PLAYER

Dear Nystagmus Network Member

We at the Research Unit for Nystagmus (R.U.N.) are currently investigating what people with nystagmus feel happens to their eyes when they are stressed.

We would like to invite you to take part in this investigation, by completing this questionnaire. We have included the answers to some frequent questions on the following pages.

What am I expected to do?

All we require is that you complete the attached questionnaire and return it to us in the stamped addressed envelope provided.

Some of the questions require you to place a mark on a line. Imagine the lines as a continuous scale from "Not at all" to "Very much so" and then place a mark on the line to indicate how much that particular statement applies to you. An example is shown below.

Not at all ⊢——————————————————————⊣ **Very much so**

Confidentiality: who will know I am taking part in this study?

All information that is collected about you during the course of the research will be kept strictly confidential. Any information about you will be encoded so that you cannot be recognized from it.

Ethics

This study has been approved by the Cardiff School of Optometry and Vision Sciences Human Research Ethics committee.

What will happen to the results of this study?

We aim to publish the results of this research in scientific journals. If you are interested, we can also summarise the results in an information sheet for you.

The research unit also carries out various other research projects at the University department in Cardiff. New volunteers are always welcome. If you would like further information, or if you have any questions or queries regarding this study, please feel free to contact me on the E-mail address or telephone number below. Many thanks for your continued support of R.U.N.

Phil Jones

JonesPH@cf.ac.uk

Tel: 02920 870556

The Impact of Stress on Nystagmus

Section 1

Please tell us a little bit about your nystagmus

1. At what age were you first diagnosed with nystagmus?

   .....

2. Have you ever been told that your nystagmus is associated/caused by any other eye conditions?

   ☐ YES

   ☐ NO

If YES, please let us know what conditions

.....
.....
.....
.....
.....
.....

Section 2

Please take a moment to give us an idea of what your vision is like. Included with this questionnaire is an A3 photocopy of a sight test chart. Please ask someone to hold this chart **4 metres** away from you. Then read down as far as you can, and circle the lowest line you can read with a pen. Please send the chart back to us with the questionnaire.

Section 3

1. Below is a list of scenarios that some people find stressful. Please read the scenarios carefully and put a mark on the line to indicate how stressful you find each.

Finding your way around an unknown place

Not at all ⊢——————————————————⊣ Very much so

Meeting new people

Not at all ⊢——————————————————⊣ Very much so

Finding products on a shelf in a supermarket

Not at all ⊢——————————————————⊣ Very much so

Crossing roads in heavy traffic

Not at all ⊢——————————————————⊣ Very much so

Finding a person in a crowd

Not at all ⊢——————————————————⊣ Very much so

Pressure at work/university/college

Not at all ⊢——————————————————⊣ Very much so

Exams/Studying

Not at all ⊢——————————————————⊣ Very much so

Being late for something

Not at all ⊢——————————————————⊣ Very much so

Speaking in public

Not at all ⊢——————————————————⊣ Very much so

Other (please specify).....

.....

.....

Not at all ⊢——————————————————⊣ Very much so

2. Thinking of the situation you identified as the **most** stressful above, how do you feel your eyes/vision are affected? Please put a mark on the lines below to indicate how much each of the following applies to you.

Difficulty seeing details / facial features

Not at all ⊢——————————————————⊣ Very much so

Things won't stay still long enough for me to see them

Not at all ⊢——————————————————⊣ Very much so

Everything blends into one

Not at all ⊢——————————————————⊣ Very much so

I take longer to see things

Not at all ├──┤ Very much so

Things become blurred / defocused

Not at all ├──┤ Very much so

I can't focus on anything

Not at all ├──┤ Very much so

Things appear to move

Not at all ├──┤ Very much so

Other (please specify)

.....

Not at all ├──┤ Very much so

Section 4

If you have any other comments about how you feel you are affected by stress, please let us know here:

.....
.....
.....
.....
.....

Contact Details

Name: .....

Address:

.....

.....

.....

.....

.....

E-Mail: .....

Home Phone: .....

Mobile: .....

If you would like to be contacted about taking part in any future research carried out by the Research Unit for Nystagmus at Cardiff University, please place a tick in the box below.

I would like to be contacted about future research ☐

Thank You

Appendix VIb: Raw data from the questionnaires returned from the investigation into the effects of stress on nystagmus

ID	Age	VA	Situations									
			Unknown Place	Meeting People	Supermarket	Crossing Road	Finding Person	Pressure	Exams	Being Late	Public Speaking	Average for Situations
1	12	0.3	18	13	12	18	46	17	16	72	27	26.56
2	-	0.4	27	10	1	0	48	11	0	24	13	14.89
3	14	0.1	1	2	22	74	6	34	52	9	7	23.00
4	81	0.7	62	13	1	46	81	45	57	56	80	49.00
5	-	0.4	18	43	14	89	93	6	20	91	16	43.33
6	37	1	88	48	79	50	95	22	16	48	53	55.44
7	36	0.6	44	4	46	47	68	11	39	15	14	32.00
8	44	1	98	46	98	99	100	81	81	76	33	79.11
9	46	0.7	63	9	17	98	75	50	49	91	21	52.56
10	20	0.4	69	40	76	90	99	21	21	26	92	59.33
11	-	0.7	75	17	7	85	83	21	13	12	17	36.67
12	14	1	81	55	96	100	100	80	60	66	17	72.78
13	9	0.5	86	93	67	94	96	0	0	80	80	66.22
14	41	0.9	92	55	67	73	70	44	10	45	27	53.67
15	9	0.5	53	1	100	100	100	56	78	0	100	65.33
16	70	0.6	23	3	23	4	25	4	26	28	4	15.56
17	18	0.7	96	0	27	90	94	52	12	91	9	52.33
18	17	0.6	40	8	40	87	84	18	16	53	7	39.22
19	63	-	74	92	97	91	97	99	98	44	98	87.78
20	59	0.6	72	13	85	93	89	0	46	93	11	55.78
21	47	0.8	82	80	98	82	96	97	93	97	96	91.22
22	59	0.6	75	72	60	70	90	95	90	88	98	82.00
23	20	0.1	4	21	3	5	4	48	78	14	45	24.67
24	-	0.4	81	22	80	70	63	83	84	15	19	57.44

Appendix VIb: Raw data from the questionnaires returned from the investigation into the effects of stress on nystagmus

ID	Age	VA	Situations									
			Unknown Place	Meeting People	Supermarket	Crossing Road	Finding Person	Pressure	Exams	Being Late	Public Speaking	Average for Situations
25	10	0.7	47	86	75	55	91	0	81	20	71	58.44
26	54	-	35	57	55	42	65	47	74	63	9	49.67
27	12	0.5	46	41	21	81	79	55	53	53	65	54.89
28	20	0.9	74	85	61	70	93	55	55	61	92	71.78
29	-	-	74	32	5	14	88	18	20	11	13	30.56
30	27	0.9	83	52	52	94	92	92	72	94	63	77.11
31	81	0.8	84	24	20	84	100	-	-	61	9	54.57
32	69	-	96	95	97	97	98	-	-	97	97	96.71
33	46	0.6	77	87	82	97	100	99	94	100	63	88.78
34	17	0.9	89	58	5	48	60	9	30	47	82	47.56
35	55	0.4	18	1	1	15	16	37	31	32	1	16.89
36	10	0.1	76	91	8	4	52	85	89	72	31	56.44
37	8	0.6	97	67	98	98	97	49	48	54	97	78.33
38	-	0.7	76	76	65	65	91	84	80	76	12	69.44
39	16	0.6	97	51	49	99	99	99	99	41	47	75.67
40	46	0.9	42	50	96	53	52	46	20	95	98	61.33
41	81	0.7	80	38	25	75	74	-	52	75	31	56.25
42	23	0.2	83	23	2	16	93	86	30	4	11	38.67
43	15	0.7	0	0	0	45	99	43	59	99	98	49.22
44	57	0.4	89	65	55	87	70	56	58	96	64	71.11
45	31	0.8	94	71	20	52	52	-	-	77	50	59.43
46	65	0.5	70	70	70	99	73	16	25	8	35	51.78
47	-	0.3	85	1	45	1	98	43	41	6	2	35.78
48	23	-	52	6	51	50	86	73	90	60	32	55.56

Appendix VIb: Raw data from the questionnaires returned from the investigation into the effects of stress on nystagmus

ID	Age	VA	Situations									
			Unknown Place	Meeting People	Supermarket	Crossing Road	Finding Person	Pressure	Exams	Being Late	Public Speaking	Average for Situations
49	12	0.4	15	13	56	58	74	85	25	13	73	45.78
50	49	0.4	71	70	31	96	72	77	78	75	95	73.89
51	67	0.5	80	17	83	94	95	73	81	65	99	76.33
52	67	0.4	86	52	66	67	99	24	30	76	23	58.11
53	9	0.6	47	6	22	95	85	-	59	12	17	42.88
54	27	0.9	83	52	80	73	96	-	-	89	23	70.86
55	47	0.9	63	76	50	79	57	71	72	41	52	62.33
56	72	0.8	72	26	94	91	95	17	42	88	36	62.33
57	50	0.6	77	53	51	59	38	58	-	23	70	53.63
58	-	0.1	71	24	86	85	95	92	91	90	94	80.89
59	50	0.9	81	12	59	95	66	59	49	61	95	64.11
60	58	0.7	12	18	18	18	64	84	71	74	88	49.67
61	68	0.6	18	0	4	70	70	19	18	92	2	32.56
62	3	0.8	96	97	98	99	99	-	88	47	98	90.25
63	44	0.6	39	45	67	87	81	19	26	22	9	43.89
64	47	0.6	30	32	30	10	38	35	26	22	61	31.56
65	36	0.8	78	52	32	48	84	29	26	16	19	42.67
66	14	0.3	18	7	78	91	8	94	99	4	99	55.33
67	-	0.8	70	69	55	90	98	78	89	72	22	71.44
68	60	0.8	86	50	68	81	82	31	31	87	37	61.44
69	14	0.2	10	50	51	34	69	72	39	22	64	45.67
70	61	0.9	92	65	32	58	92	51	72	33	27	58.00
71	-	0.7	14	58	36	99	100	91	87	93	99	75.22
72	9	0.6	70	96	87	92	96	-	97	-	96	90.57

Appendix VIb: Raw data from the questionnaires returned from the investigation into the effects of stress on nystagmus

ID	Age	VA	Situations									
			Unknown Place	Meeting People	Supermarket	Crossing Road	Finding Person	Pressure	Exams	Being Late	Public Speaking	Average for Situations
73	-	0.7	19	27	17	29	51	20	19	24	53	28.78
74	50	0.3	17	20	3	36	19	37	4	69	70	30.56
75	16	0.3	30	37	63	52	65	85	82	77	44	59.44
76	-	0.3	30	68	27	78	74	89	23	73	86	60.89
77	20	0.7	50	23	53	42	97	94	95	33	16	55.89
78	-	0.1	93	71	12	97	96	32	55	77	98	70.11
79	9	0	48	77	2	82	94	100	100	18	100	69.00
80	63	0.5	46	90	75	77	93	55	85	86	91	77.56
81	57	0.2	83	79	80	97	96	45	57	74	94	78.33
82	59	0.5	77	82	78	94	84	51	94	96	97	83.67
83	15	0.5	81	11	10	91	100	30	14	8	54	44.33
84	40	0.4	7	8	31	22	73	42	62	11	64	35.56
85	-	0.2	62	23	9	42	78	52	70	87	77	55.56
86	10	0.4	24	75	55	32	56	55	24	48	19	43.11
87	7	0.4	58	5	39	66	85	67	69	73	87	61.00
88	51	0.7	43	50	50	6	97	98	67	78	98	65.22
89	16	-	2	3	2	2	15	45	48	2	20	15.44
90	-	0.7	12	1	1	8	3	18	11	4	6	7.11
91	8	0.5	70	13	88	97	96	50	-	-	63	68.14
92	24	-	17	34	11	14	51	68	50	12	45	33.56
93	26	0.3	74	62	62	62	62	74	87	41	77	66.78
94	19	0.6	62	88	19	83	98	85	100	22	99	72.89
95	12	-	73	26	51	53	58	-	83	74	18	54.50
96	-	0.5	33	22	77	98	99	93	100	73	40	70.56

Appendix VIb: Raw data from the questionnaires returned from the investigation into the effects of stress on nystagmus

ID	Age	VA	Situations									
			Unknown Place	Meeting People	Supermarket	Crossing Road	Finding Person	Pressure	Exams	Being Late	Public Speaking	Average for Situations
97	-	0.6	82	19	85	88	21	17	16	16	14	39.78
98	-	0.4	92	27	45	68	89	37	73	10	93	59.33
99	52	0.4	64	64	88	67	93	63	47	82	68	70.67
100	40	0.7	97	5	96	76	98	75	50	100	81	75.33
101	9	0.2	46	45	8	99	57	4	4	44	10	35.22
102	47	0.5	12	13	11	12	27	18	32	17	11	17.00
103	45	0.4	64	23	25	62	93	77	94	32	28	55.33
104	60	0.9	80	68	68	96	84	83	16	13	62	63.33
105	-	0.3	65	65	2	53	43	35	59	71	84	53.00
106	27	0.5	64	94	32	85	97	94	97	36	89	76.44
107	19	0.5	73	26	63	83	94	29	54	7	20	49.89
108	16	0.8	81	7	64	84	82	17	49	51	7	49.11
109	15	0.4	26	19	17	2	71	32	18	33	3	24.56
110	11	0.2	15	65	29	61	79	53	32	14	17	40.56
111	13	0.7	98	95	68	97	100	80	98	98	69	89.22
112	14	0.7	23	7	20	77	83	26	79	48	38	44.56
113	66	0.3	52	7	33	53	92	75	81	66	10	52.11
114	20	0.3	53	6	17	21	70	8	11	6	5	21.89
115	-	0.7	12	14	12	33	84	17	28	84	32	35.11
116	45	0.6	55	18	15	5	86	13	19	85	4	33.33
117	22	0.7	72	28	80	21	96	53	38	8	62	50.89
118	-	0.5	46	15	14	59	59	72	50	28	20	40.33
119	17	0.6	46	74	35	55	82	13	13	24	55	44.11
120	15	0.2	70	43	52	96	98	46	74	43	3	58.33

Appendix VIb: Raw data from the questionnaires returned from the investigation into the effects of stress on nystagmus

ID	Age	VA	Situations									
			Unknown Place	Meeting People	Supermarket	Crossing Road	Finding Person	Pressure	Exams	Being Late	Public Speaking	Average for Situations
121	-	-	71	72	83	96	98	90	3	96	33	71.33
122	-	-	22	10	22	-	48	-	-	-	-	25.50
123	14	0.1	13	1	0	75	76	15	79	35	71	40.56
124	57	0.1	48	15	22	99	68	100	21	43	0	46.22
125	39	0.6	57	21	62	52	88	21	26	76	50	50.33
126	47	-	93	95	93	62	90	-	-	55	98	83.71
127	17	0.2	23	20	1	11	4	23	17	3	23	13.89
128	32	0.2	96	94	96	96	100	100	100	48	100	92.22
129	-	0.2	83	86	62	34	93	73	62	73	87	72.56
130	42	0.7	80	56	88	82	87	14	10	79	8	56.00
131	69	-	95	96	94	98	99	45	44	94	96	84.56
132	13	0.5	75	11	61	48	92	36	93	11	28	50.56
133	-	0.7	65	72	49	78	80	46	64	47	51	61.33
134	-	0.5	75	29	51	75	93	45	52	22	30	52.44
135	22	0.8	97	96	67	96	97	97	95	96	-	92.63
136	51	0.6	57	62	39	74	87	86	24	48	75	61.33
137	15	0.7	55	72	4	53	71	30	42	78	74	53.22
138	54	0.6	94	81	77	92	92	-	-	92	99	89.57
139	14	0.4	90	34	92	85	98	79	84	7	57	69.56
140	11	0.6	53	25	78	82	86	63	98	78	24	65.22
141	55	-	89	92	92	93	95	83	88	54	16	78.00
142	18	0.5	21	5	32	24	51	43	54	2	15	27.44
143	35	0.9	92	88	70	88	88	60	27	88	87	76.44
144	54	0.9	88	76	79	83	93	88	76	89	81	83.67

Appendix VIb: Raw data from the questionnaires returned from the investigation into the effects of stress on nystagmus

ID	Age	VA	Situations									
			Unknown Place	Meeting People	Supermarket	Crossing Road	Finding Person	Pressure	Exams	Being Late	Public Speaking	Average for Situations
145	60	0.4	81	76	86	84	98	96	95	89	90	88.33
146	-	0.5	63	21	12	59	83	59	26	4	43	41.11
147	38	0.4	68	69	33	82	85	42	21	25	81	56.22
148	70	0.14	89	3	51	88	80	15	15	91	3	48.33
149	16	0.16	39	0	82	98	91	4	35	56	10	46.11
150	46	0.4	24	74	30	61	91	22	32	69	89	54.67
151	64	0.3	29	52	28	52	48	50	10	2	24	32.78
152	12	0.5	30	1	2	100	100	56	80	88	2	51.00
153	42	0.4	65	58	56	92	75	76	65	86	98	74.56
154	-	0.7	94	23	94	94	94	-	-	95	95	84.14
155	20	0.5	80	70	71	55	87	64	75	67	68	70.78
156	-	0.6	53	52	96	94	95	41	51	9	1	54.67
157	-	-0.1	7	20	0	15	35	1	18	49	68	23.67
158	14	0.2	81	26	35	87	79	52	34	11	50	50.56
159	7	0.1	77	75	46	80	98	73	81	69	70	74.33
160	-	0.3	0	2	0	0	51	51	-	1	10	14.38
161	54	0.5	50	21	26	50	70	68	44	40	79	49.78
162	-	0.9	93	63	81	88	92	96	98	74	86	85.67
163	16	0.4	65	3	75	48	81	87	93	62	50	62.67
164	33	0.7	78	60	57	56	98	84	78	82	73	74.00

Table 1: Raw data for subjects with nystagmus to the questions regarding stressful situations

Appendix VIb: Raw data from the questionnaires returned from the investigation into the effects of stress on nystagmus

ID	Visual Consequences							
	Facial Detail	Won't Stay Still	Blends Into One	Take Longer to See	Blurred	Can't Focus	Things Move	Average for Visual
1	18	20	7	15	15	20	12	15.29
2	72	49	50	100	13	0	0	40.57
3	50	35	31	42	31	0	0	27.00
4	52	90	28	81	67	15	15	49.71
5	90	26	40	91	33	34	26	48.57
6	95	47	57	65	81	33	33	58.71
7	62	44	29	73	57	15	65	49.29
8	96	83	60	99	99	65	69	81.57
9	85	33	36	98	53	4	55	52.00
10	92	23	22	96	51	22	17	46.14
11	61	5	12	57	6	12	10	23.29
12	100	80	69	73	94	60	91	81.00
13	78	75	78	81	81	67	80	77.14
14	88	95	74	81	41	76	70	75.00
15	59	100	100	4	59	84	69	67.86
16	63	5	59	46	13	28	6	31.43
17	71	80	73	76	73	29	34	62.29
18	21	45	62	60	64	10	9	38.71
19	98	60	88	70	93	92	93	84.86
20	93	93	88	92	90	42	35	76.14
21	97	98	95	96	97	78	80	91.57
22	84	52	51	85	60	70	83	69.29
23	33	35	8	35	35	0	34	25.71
24	79	96	0	80	84	95	16	64.29
25	95	67	65	77	84	25	38	64.43

Appendix VIb: Raw data from the questionnaires returned from the investigation into the effects of stress on nystagmus

ID	Visual Consequences							
	Facial Detail	Won't Stay Still	Blends Into One	Take Longer to See	Blurred	Can't Focus	Things Move	Average for Visual
26	81	9	11	66	8	6	9	27.14
27	39	69	20	58	16	39	61	43.14
28	77	43	26	71	58	8	5	41.14
29	79	21	12	67	25	24	22	35.71
30	91	78	59	87	59	61	96	75.86
31	94	4	5	6	6	7	6	18.29
32	95	96	97	96	97	98	97	96.57
33	100	99	65	98	89	68	71	84.29
34	11	47	16	3	27	2	2	15.43
35	31	12	2	34	34	55	0	24.00
36	3	48	2	48	64	16	82	37.57
37	98	3	5	97	98	99	97	71.00
38	83	20	52	76	74	16	66	55.29
39	26	34	36	99	96	94	97	68.86
40	98	96	3	98	100	52	47	70.57
41	78	85	68	71	0	31	59	56.00
42	60	9	14	30	26	4	5	21.14
43	97	94	3	96	51	85	18	63.43
44	100	82	84	100	100	100	1	81.00
45	99	15	50	89	83	52	5	56.14
46	75	99	27	96	22	21	98	62.57
47	3	38	41	41	43	41	2	29.86
48	28	55	68	83	78	79	78	67.00
49	74	33	39	94	93	42	25	57.14
50	95	28	68	82	30	78	30	58.71

Appendix VIb: Raw data from the questionnaires returned from the investigation into the effects of stress on nystagmus

ID	Visual Consequences							
	Facial Detail	Won't Stay Still	Blends Into One	Take Longer to See	Blurred	Can't Focus	Things Move	Average for Visual
51	95	90	73	81	84	83	86	84.57
52	76	28	23	78	28	70	81	54.86
53	79	68	82	55	80	71	35	67.14
54	94	94	93	89	91	52	66	82.71
55	69	66	67	69	56	39	53	59.86
56	90	31	8	92	15	5	21	37.43
57	76	25	45	78	68	64	22	54.00
58	96	96	94	92	94	95	95	94.57
59	92	68	74	93	92	90	60	81.29
60	84	8	8	86	84	11	11	41.71
61	35	51	0	95	2	2	97	40.29
62	98	99	65	89	76	50	51	75.43
63	86	18	18	79	15	9	17	34.57
64	37	6	5	26	7	5	4	12.86
65	81	81	51	75	39	38	55	60.00
66	87	80	51	100	97	96	80	84.43
67	89	53	95	95	58	25	24	62.71
68	92	58	9	92	64	47	77	62.71
69	94	40	12	74	68	46	48	54.57
70	87	56	11	-	79	77	29	56.50
71	100	99	2	99	53	100	97	78.57
72	-	91	-	92	60	93	91	85.40
73	71	7	74	82	44	15	7	42.86
74	38	0	0	64	1	1	1	15.00
75	36	34	34	65	54	52	17	41.71

Appendix VIb: Raw data from the questionnaires returned from the investigation into the effects of stress on nystagmus

ID	Visual Consequences							
	Facial Detail	Won't Stay Still	Blends Into One	Take Longer to See	Blurred	Can't Focus	Things Move	Average for Visual
76	69	40	37	70	69	17	25	46.71
77	100	95	19	100	79	93	77	80.43
78	75	12	0	70	68	2	6	33.29
79	94	61	78	78	96	61	22	70.00
80	95	65	44	85	91	40	12	61.71
81	69	72	72	76	83	85	90	78.14
82	51	85	98	72	78	39	92	73.57
83	86	78	42	88	98	57	15	66.29
84	42	20	38	97	21	3	17	34.00
85	30	48	20	66	47	10	27	35.43
86	6	76	75	91	85	5	20	51.14
87	17	69	49	62	69	27	27	45.71
88	97	50	47	91	91	96	48	74.29
89	9	0	1	2	23	1	1	5.29
90	1	1	1	4	15	3	1	3.71
91	87	44	74	73	48	10	52	55.43
92	94	21	37	76	91	93	72	69.14
93	51	58	20	66	55	23	23	42.29
94	86	8	48	86	22	36	12	42.57
95	25	58	8	50	21	4	8	24.86
96	98	98	77	83	96	98	89	91.29
97	86	68	87	86	87	69	75	79.71
98	93	92	89	64	91	19	73	74.43
99	75	37	50	86	18	55	19	48.57
100	99	99	57	100	61	45	67	75.43

Appendix VIb: Raw data from the questionnaires returned from the investigation into the effects of stress on nystagmus

ID	Visual Consequences							
	Facial Detail	Won't Stay Still	Blends Into One	Take Longer to See	Blurred	Can't Focus	Things Move	Average for Visual
101	50	2	48	50	50	0	15	30.71
102	42	8	14	44	15	14	6	20.43
103	96	62	29	67	26	24	50	50.57
104	92	11	11	55	41	43	5	36.86
105	29	10	9	48	72	79	44	41.57
106	100	19	15	90	29	28	13	42.00
107	57	60	30	80	73	40	47	55.29
108	89	66	90	84	58	27	54	66.86
109	54	39	17	76	45	30	7	38.29
110	88	64	40	61	21	87	21	54.57
111	53	88	94	83	96	95	93	86.00
112	19	63	12	47	47	12	10	30.00
113	82	80	11	88	53	15	10	48.43
114	89	2	0	68	14	0	1	24.86
115	99	49	31	57	6	5	4	35.86
116	91	83	75	56	83	76	26	70.00
117	72	26	63	85	33	46	25	50.00
118	72	94	78	78	85	91	64	80.29
119	46	46	26	63	66	72	8	46.71
120	96	94	6	61	95	42	44	62.57
121	92	91	92	94	91	70	95	89.29
122	29	31	5	63	62	46	16	36.00
123	23	1	10	15	46	0	5	14.29
124	99	100	100	100	99	100	0	85.43
125	84	47	62	69	66	44	14	55.14

Appendix VIb: Raw data from the questionnaires returned from the investigation into the effects of stress on nystagmus

ID	Visual Consequences							
	Facial Detail	Won't Stay Still	Blends Into One	Take Longer to See	Blurred	Can't Focus	Things Move	Average for Visual
126	97	91	3	95	95	94	49	74.86
127	48	0	1	53	1	3	2	15.43
128	86	100	99	100	100	100	100	97.86
129	83	10	4	47	6	8	5	23.29
130	97	20	14	96	12	6	8	36.14
131	98	39	26	78	22	9	40	44.57
132	83	66	46	64	85	51	35	61.43
133	62	46	46	63	51	27	41	48.00
134	75	52	54	59	63	23	19	49.29
135	97	94	94	96	94	76	92	91.86
136	92	82	69	83	79	79	75	79.86
137	59	78	35	72	16	13	33	43.71
138	83	97	48	91	57	57	91	74.86
139	95	92	65	64	96	17	24	64.71
140	69	46	29	50	30	10	33	38.14
141	95	45	57	90	60	60	7	59.14
142	37	4	12	34	32	4	5	18.29
143	83	45	1	87	83	51	81	61.57
144	85	85	86	93	92	91	92	89.14
145	91	89	84	95	94	96	95	92.00
146	97	81	8	99	87	70	1	63.29
147	78	55	39	74	70	40	36	56.00
148	84	97	6	91	10	48	3	48.43
149	5	76	5	85	43	5	36	36.43
150	73	56	16	58	13	13	20	35.57

Appendix VIb: Raw data from the questionnaires returned from the investigation into the effects of stress on nystagmus

ID	Visual Consequences							
	Facial Detail	Won't Stay Still	Blends Into One	Take Longer to See	Blurred	Can't Focus	Things Move	Average for Visual
151	82	62	20	34	60	14	71	49.00
152	98	98	17	99	100	84	99	85.00
153	71	57	14	72	32	75	1	46.00
154	96	93	92	94	94	44	94	86.71
155	89	82	79	85	85	69	63	78.86
156	99	46	97	32	93	0	92	65.57
157	0	4	5	6	12	16	19	8.86
158	78	86	47	86	84	87	79	78.14
159	39	24	22	12	50	19	18	26.29
160	20	0	0	78	1	1	0	14.29
161	92	28	26	68	30	31	28	43.29
162	81	81	58	69	91	95	76	78.71
163	56	56	6	87	94	52	44	56.43
164	91	61	54	96	25	51	16	56.29

Table 2: Raw data for subjects with nystagmus to the questions regarding visual consequences to stressful situations

Appendix VIb: Raw data from the questionnaires returned from the investigation into the effects of stress on nystagmus

ID	Age	VA	Situations									
			Unknown Place	Meeting People	Supermarket	Crossing Road	Finding Person	Pressure	Exams	Being Late	Public Speaking	Average for Situations
1	49	-0.1	57	58	3	31	35	51	53	78	70	48.44
2	49	0.1	0	16	0	14	97	0	-	2	90	27.38
3	43	-0.1	46	94	43	3	4	45	94	91	93	57.00
4	40	0.2	52	74	8	9	7	6	9	15	82	29.11
5	25	-0.1	0	100	18	77	62	7	49	95	2	45.56
6	-	-	2	3	3	2	1	1	-	100	99	26.38
7	29	-0.1	60	22	20	35	34	96	98	77	99	60.11
8	51	-0.1	50	31	3	20	37	46	31	85	82	42.78
9	51	0.1	23	2	25	3	4	44	74	96	3	30.44
10	40	-0.2	0	0	0	20	2	2	51	33	53	17.89
11	31	0.0	25	3	7	4	7	33	9	80	5	19.22
12	32	0.0	53	0	24	4	30	86	50	96	68	45.67
13	29	0.0	55	67	38	86	77	70	100	84	100	75.22
14	20	-0.2	68	26	18	4	43	89	92	3	46	43.22
15	19	0.0	29	23	0	0	6	6	52	100	0	24.00
16	12	0.0	56	24	1	5	9	3	5	72	18	21.44
17	14	-0.1	28	6	23	52	51	29	62	82	15	38.67
18	60	0.0	9	50	3	2	3	49	49	73	97	37.22
19	54	-0.16	5	4	14	13	16	50	24	92	16	26.00
20	43	0.0	31	59	8	52	47	55	70	80	87	54.33
21	42	-0.2	48	16	15	3	7	50	85	81	77	42.44
22	14	-0.1	49	35	31	30	40	36	38	53	64	41.78
23	25	-0.2	31	61	0	33	35	36	37	53	63	38.78
24	25	-0.2	50	50	24	51	60	63	64	83	63	56.44

Appendix VIb: Raw data from the questionnaires returned from the investigation into the effects of stress on nystagmus

ID	Age	VA	Situations									
			Unknown Place	Meeting People	Supermarket	Crossing Road	Finding Person	Pressure	Exams	Being Late	Public Speaking	Average for Situations
25	22	-0.2	16	5	6	6	31	32	38	80	95	34.33
26	14	0.2	3	2	2	2	53	21	52	4	4	15.89
27	45	0.3	30	11	10	32	17	23	60	64	71	35.33
28	73	0.4	29	42	91	90	92	-	-	93	92	75.57
29	11	-0.2	11	0	0	9	3	0	9	14	0	5.11
30	79	0.2	89	6	46	76	41	19	51	83	89	55.56
31	77	0.2	25	0	0	76	46	-	-	100	22	38.43
32	26	-0.2	10	51	1	3	2	6	7	20	76	19.56
33	51	0.1	47	27	4	8	28	52	-	71	93	41.25
34	52	-0.1	9	30	1	1	14	25	13	48	7	16.44
35	28	0.0	15	57	66	51	68	77	22	89	83	58.67
36	6	0.2	69	10	3	2	66	-	0	0	14	20.50
37	18	-0.1	22	85	0	22	3	78	84	59	96	49.89
38	20	0.1	35	62	4	26	39	49	74	43	93	47.22
39	38	0.1	12	2	2	21	8	50	53	50	69	29.67
40	39	-0.1	32	67	7	5	4	32	83	70	79	42.11
41	10	0.0	19	1	1	62	1	1	10	84	8	20.78
42	13	-0.1	1	1	1	49	1	1	77	99	1	25.67
43	25	0.1	23	31	4	5	45	64	46	45	28	32.33
44	43	-0.1	39	4	6	13	51	99	98	65	49	47.11
45	31	0.1	19	14	2	2	1	15	28	49	50	20.00
46	50	0.0	73	5	5	5	13	5	54	75	96	36.78
47	40	0.3	13	50	1	2	2	24	77	50	99	35.33
48	26	0.0	26	18	18	24	32	37	63	45	73	37.33

Appendix VIb: Raw data from the questionnaires returned from the investigation into the effects of stress on nystagmus

ID	Age	VA	Situations									
			Unknown Place	Meeting People	Supermarket	Crossing Road	Finding Person	Pressure	Exams	Being Late	Public Speaking	Average for Situations
49	23	-0.2	7	51	9	35	27	69	95	93	79	51.67
50	40	-0.1	2	2	1	1	1	79	80	76	24	29.56
51	38	0.6	0	0	0	0	13	16	93	97	99	35.33
52	22	-0.1	0	12	0	5	28	81	82	92	41	37.89
53	21	0.0	11	1	0	5	24	46	72	45	28	25.78
54	20	0.0	41	3	0	4	22	15	42	60	44	25.67
55	24	-0.1	27	39	7	8	13	69	98	76	77	46.00
56	21	-0.1	8	15	0	10	6	100	100	0	25	29.33
57	27	-0.1	16	32	14	6	4	77	88	52	52	37.89
58	20	0.0	63	12	12	59	46	94	97	81	71	59.44
59	22	-0.1	24	15	17	16	28	36	38	9	25	23.11
60	21	-0.2	5	14	48	7	29	64	40	71	50	36.44
61	22	-0.2	25	25	25	38	38	69	100	73	51	49.33
62	20	0.0	0	15	28	17	12	78	78	99	60	43.00
63	20	-0.2	18	5	0	0	0	53	68	20	85	27.67
64	22	-0.2	9	10	0	10	26	46	61	47	56	29.44
65	24	-0.1	37	50	8	7	18	52	51	72	87	42.44
66	22	0.0	0	6	0	4	22	63	72	99	63	36.56
67	24	-0.1	0	21	0	9	32	73	79	7	66	31.89
68	33	0.2	16	17	15	16	18	59	19	56	58	30.44
69	35	-0.1	36	31	0	0	15	29	36	38	41	25.11
70	36	0.1	35	65	11	14	38	47	50	63	78	44.56
71	24	0.0	52	45	0	0	12	49	80	89	53	42.22
72	-	-0.1	27	44	10	69	52	61	44	61	62	47.78

Appendix VIb: Raw data from the questionnaires returned from the investigation into the effects of stress on nystagmus

ID	Age	VA	Situations									
			Unknown Place	Meeting People	Supermarket	Crossing Road	Finding Person	Pressure	Exams	Being Late	Public Speaking	Average for Situations
73	25	0.3	44	84	13	37	66	86	51	33	100	57.11
74	35	0.0	52	18	0	48	17	75	76	78	11	41.67
75	28	-0.2	49	99	1	34	34	45	82	89	88	57.89
76	37	-0.1	9	10	9	11	12	52	53	90	87	37.00
77	36	-0.2	23	22	19	7	12	29	29	28	45	23.78
78	43	-0.1	53	62	4	19	52	57	57	59	80	49.22
79	25	0.0	11	24	0	40	20	66	84	76	56	41.89
80	24	0.1	55	41	10	49	22	51	38	70	82	46.44
81	46	0.0	0	34	25	32	14	12	15	92	64	32.00
82	31	-0.1	29	26	9	34	28	47	57	67	13	34.44
83	36	-0.1	19	6	10	13	27	30	35	38	66	27.11
84	33	0.0	45	50	4	55	37	71	10	74	74	46.67
85	-	-0.1	7	11	0	8	5	25	18	16	28	13.11
86	24	0.2	0	0	0	0	9	52	85	65	100	34.56
87	23	-0.2	72	73	2	64	73	96	97	75	92	71.56
88	23	-0.2	17	6	47	15	49	66	86	66	8	40.00
89	20	0.0	25	47	9	53	54	43	77	80	62	50.00
90	37	-0.2	6	47	39	38	46	61	33	30	73	41.44
91	55	-0.1	25	24	25	46	29	0	-	74	53	34.50
92	44	0.0	0	13	13	15	11	15	61	55	65	27.56
93	-	-0.2	62	55	45	46	50	23	86	75	98	60.00
94	27	-0.1	9	25	8	11	13	36	46	49	31	25.33
95	27	-0.2	34	3	2	70	24	76	77	72	52	45.56
96	23	-0.1	47	12	1	51	37	82	92	53	14	43.22

Appendix VIb: Raw data from the questionnaires returned from the investigation into the effects of stress on nystagmus

ID	Age	VA	Situations									
			Unknown Place	Meeting People	Supermarket	Crossing Road	Finding Person	Pressure	Exams	Being Late	Public Speaking	Average for Situations
97	21	-0.1	5	8	1	4	12	76	100	58	21	31.67
98	31	-0.1	4	14	0	4	3	94	99	65	99	42.44
99	21	-0.1	17	11	0	4	33	69	87	43	39	33.67
100	30	-0.2	42	32	64	53	81	5	48	32	10	40.78
101	37	-0.2	75	72	4	56	55	68	52	69	85	59.56
102	21	-0.1	0	6	0	0	0	87	100	24	100	35.22
103	25	0.0	0	0	0	20	1	50	82	58	23	26.00

Table 3: Raw data for control subjects to the questions regarding stressful situations

Appendix VIb: Raw data from the questionnaires returned from the investigation into the effects of stress on nystagmus

ID	Visual Consequences							
	Facial Detail	Won't Stay Still	Blends Into One	Take Longer to See	Blurred	Can't Focus	Things Move	Average for Visual
1	26	10	8	31	23	18	19	19.29
2	26	15	0	1	1	1	1	6.43
3	6	52	6	7	12	11	10	14.86
4	81	83	83	78	82	82	85	82.00
5	0	10	0	0	15	0	0	3.57
6	2	1	3	2	1	1	0	1.43
7	0	0	0	25	26	26	3	11.43
8	6	3	21	65	82	80	6	37.57
9	94	11	50	74	75	10	12	46.57
10	0	0	0	0	0	0	0	0.00
11	15	25	10	20	10	7	18	15.00
12	3	0	0	10	9	2	0	3.43
13	81	81	79	78	14	18	65	59.43
14	11	40	0	32	31	0	41	22.14
15	0	9	0	0	0	0	0	1.29
16	52	1	42	52	62	9	5	31.86
17	0	0	0	0	0	0	0	0.00
18	4	4	13	22	23	23	22	15.86
19	8	7	6	5	4	3	3	5.14
20	19	24	18	11	13	8	8	14.43
21	60	54	61	49	38	30	35	46.71
22	24	24	23	25	22	29	24	24.43
23	0	1	1	0	0	0	1	0.43
24	82	0	1	0	40	0	0	17.57
25	4	0	3	14	9	7	0	5.29

Appendix VIb: Raw data from the questionnaires returned from the investigation into the effects of stress on nystagmus

ID	Visual Consequences							
	Facial Detail	Won't Stay Still	Blends Into One	Take Longer to See	Blurred	Can't Focus	Things Move	Average for Visual
26	2	3	5	19	30	13	2	10.57
27	60	67	66	60	64	58	68	63.29
28	0	56	0	63	0	0	0	17.00
29	0	0	0	0	0	0	0	0.00
30	0	0	0	0	0	0	0	0.00
31	74	81	5	92	90	20	84	63.71
32	0	0	0	1	0	0	2	0.43
33	10	2	3	22	12	6	3	8.29
34	3	2	2	2	4	3	3	2.71
35	3	3	6	23	6	8	5	7.71
36	0	0	0	0	1	0	0	0.14
37	97	79	90	51	70	82	15	69.14
38	1	9	0	3	18	0	9	5.71
39	0	0	0	0	0	0	0	0.00
40	4	6	10	7	8	6	5	6.57
41	1	1	1	1	1	2	2	1.29
42	1	1	1	1	1	1	1	1.00
43	4	4	0	5	5	3	0	3.00
44	60	11	3	99	52	9	6	34.29
45	3	4	5	7	6	4	5	4.86
46	3	4	3	2	3	3	3	3.00
47	88	57	56	78	77	24	23	57.57
48	13	16	19	22	19	19	16	17.71
49	4	2	3	4	3	5	6	3.86
50	1	1	2	1	2	1	1	1.29

Appendix VIb: Raw data from the questionnaires returned from the investigation into the effects of stress on nystagmus

ID	Visual Consequences							
	Facial Detail	Won't Stay Still	Blends Into One	Take Longer to See	Blurred	Can't Focus	Things Move	Average for Visual
51	71	3	3	6	71	3	2	22.71
52	0	0	0	0	0	0	0	0.00
53	0	0	0	0	0	0	0	0.00
54	3	3	3	3	4	3	3	3.14
55	19	0	0	1	1	0	0	3.00
56	0	0	0	0	0	0	0	0.00
57	3	2	2	1	84	1	1	13.43
58	18	0	0	0	22	0	0	5.71
59	4	2	1	3	7	2	2	3.00
60	51	0	0	15	13	0	0	11.29
61	0	0	0	0	12	0	0	1.71
62	63	0	48	57	57	0	0	32.14
63	0	0	0	0	0	0	0	0.00
64	0	0	0	0	0	0	0	0.00
65	7	0	0	50	0	0	0	8.14
66	0	0	0	0	0	0	0	0.00
67	58	6	51	26	68	38	54	43.00
68	4	3	5	6	5	5	5	4.71
69	1	2	2	2	2	2	2	1.86
70	46	15	45	33	17	21	22	28.43
71	0	0	1	0	1	0	0	0.29
72	0	0	0	2	7	3	0	1.71
73	81	52	91	60	100	61	14	65.57
74	10	0	11	30	10	0	0	8.71
75	2	2	2	2	2	2	2	2.00

Appendix VIb: Raw data from the questionnaires returned from the investigation into the effects of stress on nystagmus

ID	Visual Consequences							
	Facial Detail	Won't Stay Still	Blends Into One	Take Longer to See	Blurred	Can't Focus	Things Move	Average for Visual
76	10	0	14	25	0	20	1	10.00
77	0	0	0	0	0	0	0	0.00
78	15	0	0	6	8	0	0	4.14
79	25	0	9	9	34	0	0	11.00
80	10	17	28	20	3	10	13	14.43
81	11	10	9	50	18	1	2	14.43
82	0	0	0	0	0	0	0	0.00
83	20	3	4	5	24	4	5	9.29
84	0	0	0	0	0	0	0	0.00
85	0	0	0	0	0	0	0	0.00
86	0	0	0	16	17	0	0	4.71
87	8	1	1	26	26	1	1	9.14
88	0	70	70	73	73	28	0	44.86
89	5	6	3	2	2	2	3	3.29
90	5	14	17	16	15	25	12	14.86
91	27	26	23	28	26	29	30	27.00
92	0	0	0	1	1	0	1	0.43
93	21	15	8	13	1	11	2	10.14
94	9	8	8	10	8	6	6	7.86
95	3	3	2	2	2	2	3	2.43
96	0	0	1	1	0	0	1	0.43
97	0	0	0	0	7	3	0	1.43
98	0	0	0	0	0	0	0	0.00
99	31	24	27	7	4	3	4	14.29
100	71	20	17	72	17	17	19	33.29

Appendix VIb: Raw data from the questionnaires returned from the investigation into the effects of stress on nystagmus

ID	Visual Consequences							
	Facial Detail	Won't Stay Still	Blends Into One	Take Longer to See	Blurred	Can't Focus	Things Move	Average for Visual
101	2	3	3	4	3	3	4	3.14
102	1	1	0	0	2	2	2	1.14
103	2	0	0	0	0	0	0	0.29

Table 4: Raw data for control subjects to the questions regarding visual consequences to stressful situations