TORSIONAL OPTOKINETIC NYSTAGMUS: RESPONSE CHARACTERISTICS MEASURED IN THE NORMAL POPULATION AND PATIENTS WITH OCULAR MOTOR DISORDERS.

Thesis submitted for the degree of

Doctor of Philosophy

at the University of Leicester

By

Shegufta Jabeen Farooq B.Med.Sci. (Orthoptics) (Sheffield)

Ophthalmology Group

Department of Cardiovascular Sciences

University of Leicester

March 2008

Torsional Optokinetic Nystagmus: response characteristics measured in the normal population and patients with ocular motor disorders.

Author: Shegufta Jabeen Farooq
Supervisor: Professor Irene Gottlob
Co-supervisor: Dr. Frank Anthony Proudlock

This thesis presents the first detailed study of the torsional optokinetic nystagmus (tOKN) response in the normal population and in patients with oculomotor disorders. The effects on the tOKN response of: (i) stimulus velocity, (ii) stimulus area, and (iii) aging, were investigated in the normal population. The tOKN response was also evaluated in patients with long standing oculomotor disorders, namely strabismus and infantile nystagmus.

Torsional OKN responses were recorded using infrared video-oculography and were elicited with volunteers fixating the centre of a large-field rotating sinusoidal grating pattern.

Torsional OKN responses were present in all normal young volunteers (n=20) to stimuli rotated in clockwise and anticlockwise directions, and a linear relationship was observed between log stimulus velocity and tOKN slow phase velocity. Torsional OKN also showed brisk responses to peripheral field stimulation in the same subjects. The first report of a significant increase with age in the proportion of absent tOKN responses is also described in normal subjects aged between 19-72 years (n=30).

The tOKN response was investigated for the first time in strabismic patients (n=16), comparing horizontal and vertical OKN responses, and also in patients with infantile nystagmus (n=16). OKN responses from strabismus patients demonstrated consistent asymmetry in horizontal and vertical directions. However, a significantly higher incidence of absent tOKN responses in both intorsion and extorsion directions were observed in comparison to controls. Torsional OKN was present in 3 of 16 patients with infantile nystagmus.

Torsional OKN is a well developed reflex in the normal population with the capacity to respond in proportion to stimulus velocity and area of stimulation. However, the tOKN response is dramatically affected by (i) the effects of aging, (ii) by the interruption of binocular visual development in patients with strabismus, and (iii) by the presence of infantile nystagmus.

Acknowledgments

I would like to thank my supervisors Professor Irene Gottlob and Dr. Frank Proudlock for their invaluable assistance at all stages of this project. Their unfailing support, patience, advice, encouragement and time from the beginning to the final draft of this thesis is something I will never forget. Through both of you, I have learned so much.

I would also like to thank Rebecca Mclean for her teaching with experimental work, assistance with patient recruitment and above all for her encouragement throughout. My appreciation too for other members of the Ophthalmology group past and present. My thanks go to Jill Horsley, who was present at the beginning, Sam Kerr and M. Surenderan for their help with all administrative needs. Thank you to my research colleagues, Shery Thomas, Mazz Awan and Archana Pradeep. I am very grateful to you all for always putting a smile on my face, particularly in the latter stages of this project.

My sincere thanks also to all participants in all experiments of this thesis, without which this project would not have been possible.

Thank you to Jean Voller, all her staff at the Orthoptic Department and all paediatric and neuro-ophthalmology clinic staff at the University Hospitals of Leicester for their reassuring support and for always making my job as an orthoptist a pleasure.

Finally, heartfelt thanks to my beautiful family and friends. Special thanks to my parents, for always believing in me and my siblings and friends, for being my inspiration. This thesis is dedicated to you all.

Contents

11. Additional addenda in attached CD (CD-RW)

Contents

1. Movies (require *windows media player* to view)

Movie A: *EyesOKN.m1v*

Movie B: *Horizontal OKN.m1v*

Movie C: *Torsional OKN; clip1.m1v, clip2.m1v, clip3.m1v, clip4.m1v.*

2. Publications (require *Adobe Acrobat reader* to view)

A: *Aging*

B: *Normal Response Characteristics*

3. Appendix D: Experimental data samples

(require *Microsoft excel, Microsoft power point and SPSS(14.0 for windows)*

Experiment 1

Experiment 2

Experiment 3

Experiment 4

Experiment 5

List of Figures

List of tables

List of publications in support of this thesis.
(See appendix (A) and additional addenda CD)

(A) Farooq SJ, Gottlob I, Benskin S, Proudlock FA. The Effect of Aging on Torsional Optokinetic Nystagmus. **Investigative Ophthalmology & Visual Science.** 2008; 49(2): 589-593.

(B) Farooq SJ, Proudlock FA, Gottlob I. Torsional optokinetic nystagmus: normal response characteristics. **British Journal of Ophthalmology**. 2004 Jun; 88(6): 796-802.

Terminology and abbreviations (listed in alphabetical order)

Accommodation*: The ability of the eye to increase its dioptric power (the convexity of the crystalline lens) in order to obtain a clear image of a near object.

AI*:* Asymmetry index; in relation to OKN refers to the degree of OKN asymmetry in opposite directions of rotation, e.g. up versus down, temporalward versus nasalwardward, intorsion versus extorsion. Values close to one or zero indicate an asymmetry. Values close to 0.5 indicate no asymmetry between the two directions.

Amblyopia*: A condition of diminished visual form sense which is not the result of any clinically demonstrable anomaly of the visual pathway, and which is not relieved by the elimination of any defect which constitutes a dioptric obstacle to the formation of the foveal image.

Amplitude (A): In relation to OKN, refers to the size of the slow phase.

Beat frequency (BF): The timing of the quick phase of the OKN response.

Conjugate*: Movements of the two eyes in the same direction.

Diplopia*: The simultaneous perception of two images of one object.

Disconjugate*: Movements of the eyes in which the visual axes do not remain parallel but move in opposite relative directions.

Disparity: Unequal visual inputs due to a difference in visual acuity in each eye, induced with prisms or due to strabismus.

Esotropia*: One or other eye deviates nasally when both eyes are open.

Excyclotropia*: The eye is misaligned around the anteroposterior axis so that the top pole is deviated away from the nose.

Exotropia* : One or other eye deviates temporally when both eyes are open.

Extorsion: Rotation of the eye around the anteroposterior axis *(Ficks X axis)*, so that the upper part of the eye rotates away from the nose.

F: Female

Gain*:* The ratio of eye velocity to stimulus velocity

hOKN: Horizontal optokinetic nystagmus.

Hypertropia*: One eye is deviated upwards when both eyes are open.

Hypotropia*: One eye is deviated downwards when both eyes are open.

IIN: Idiopathic Infantile Nystagmus

IN: Infantile nystagmus

Incyclotropia*: The eye is misaligned around the anteroposterior axis so that the top pole is deviated towards the nose.

Intorsion: Rotation of the eye around the anteroposterior axis *(Ficks X axis)*, so that the upper part of the eye rotates towards the nose.

***MSPV*:** Mean slow phase velocity. In relation to OKN, refers to the average size of the slow phase over a continuous period of stimulation.

***Nasalward*:** In relation to hOKN, refers to the stimulus moving towards the subject from the periphery.

OKN: Optokinetic nystagmus.

Orthophoria*: Both visual axes are directed towards the fixation point and do not deviate on dissociation.

PP: Primary position, clinically refers to the eyes looking straight ahead at 0º.

***SPV*:** Slow phase velocity; in relation to OKN, refers to the size of the slow phase in one OKN beat.

Strabismus*: A manifest or latent ocular deviation.

Temporalward: In relation to hOKN, refers to the stimulus moving away from the subject to the periphery.

tOKN: Torsional optokinetic nystagmus.

Torsion*: Subjective appreciation of torsional distortion of an image.

Torsional: In the intorsion or extorsion direction.

vOKN: Vertical optokinetic nystagmus.

(* From: *Dictionary of Common Terms in Orthoptic Practice, Edited by Fiona Rowe © British Orthoptic Society, 2001(British Orthoptic Society 2001))*

1. Introduction

1. Introduction

1.1. Overview

Eye movements fall into two main categories, those that stabilise gaze and keep images steady on the retina, in particular the foveal area. This includes the vestibular, optokinetic and smooth pursuit systems. The second category comprises eye movements that redirect the line of sight to a new object of interest, which includes the vergence and saccadic systems (Carpenter, 1988; Buttner & Büttner-Ennever, 2006). Humans are able to move their eyes in the horizontal, vertical and torsional dimensions. Although all three dimensions of movement are possible, the horizontal and vertical dimensions have been more thoroughly researched than eye movements in the torsional direction. This is due to the availability of better techniques for recording in the horizontal and vertical dimensions.

Torsional eye movement control is a crucial component of maintaining stability of retinal images. The stabilization of the retinal image around the torsional meridian requires the coupling of the vestibular and optokinetic (OKN) systems. The torsional optokinetic (tOKN) system directly senses image motion around the torsional meridian and responds accordingly. Although there is much literature regarding the stabilisation of images in the horizontal and vertical meridian using the horizontal OKN (hOKN) and vertical OKN (vOKN) reflexes, investigations into tOKN control are scant.

The first description of the tOKN response was given by Brecher in 1934 who observed torsional movement of the eye when viewing the conjunctival blood vessels of a subject who looked at a rotating stimulus. Figure 1.1 shows the original figure demonstrating the tOKN response with related schematic illustration of the eye movement,

using an iris blood vessel as a marker. The subject demonstrates tOKN in response to clockwise stimulation.

Figure 1.1. *Original figure taken from Brecher (1934), depicting the torsional optokinetic response. The left hand picture and the below schematic iris vessel picture shows the subject making the slow phase of the tOKN response in the clockwise direction. The right hand picture depicts the eye 1/12th of a second later.*

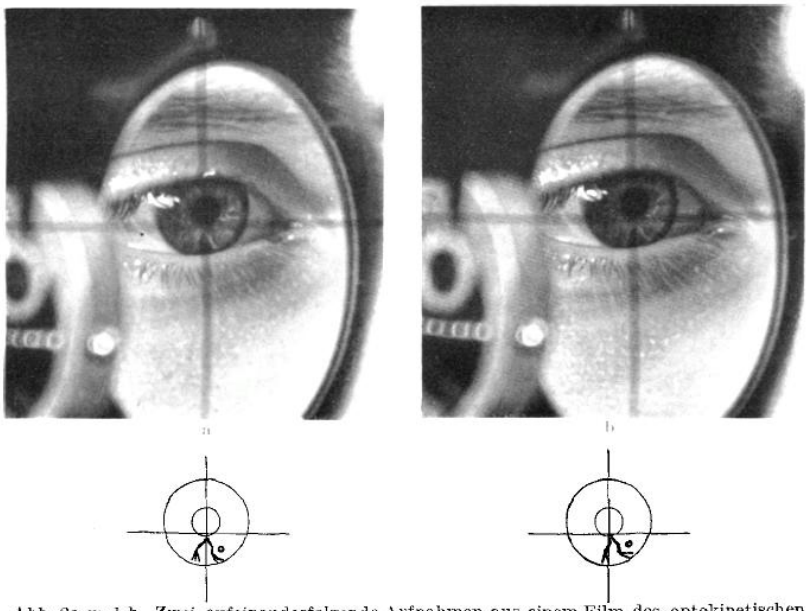


Abb. 2a und b. Zwei aufeinanderfolgende Aufnahmen aus einem Film des optokinetischen rotatorischen Nystagmus. a Stellung des Auges in maximaler Abweichung und b 1/12 Sek. später nach einem nystaktischen Rucke. Zur besseren Übersicht sind die zwei besonders deutlichen schenkelförmigen Iriskrypten und ein daneben liegender Pigmentfleck nochmals gesondert in den beiden Stellungen gezeichnet.

Some authors have questioned the presence of tOKN (Abadi & Dickinson, 1985) stating that humans do not have a torsional optokinetic response but that only a "steady torsional deviation of the eye is observed" (Kertesz & Jones, 1969).

Improvement in technology for recording torsional eye movements has enabled us to progress in our understanding of this reflex. The use of a telescope was crucial for

Brecher's first observation in 1934 as the torsional optokinetic response is much smaller in magnitude compared to the response in the horizontal and vertical meridians (Collewijn *et al.*, 1985; Cheung & Howard, 1991; Seidman *et al.*, 1992; Morrow & Sharpe, 1993; Suzuki *et al.*, 2000). Even with the advent of advanced recording techniques, the normal response characteristics have been very seldom explored in the literature. Furthermore, we have no insight in how this reflex behaves in the presence of congenital defects of the ocular motor system. It is these aspects of the torsional optokinetic response that this thesis will explore.

1.2. Eye movement systems

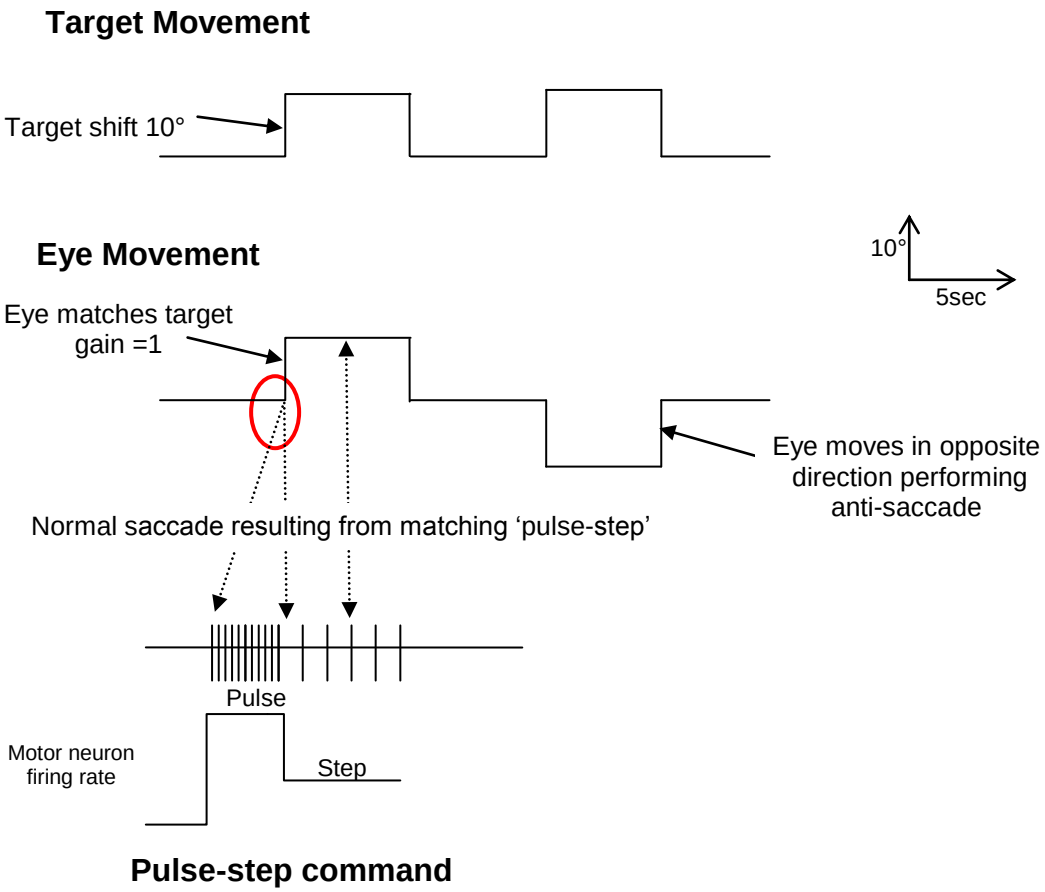
Before discussing the optokinetic system, and in particular the torsional optokinetic system, a brief overview of the other ocular motor systems is provided.

1.2.1. The Saccadic system

Saccades are rapid eye movements that redirect the line of sight to new points of fixation. Figure 1.2 shows saccadic and antisaccadic eye movements made to a 10° target jump. Their main function is to direct the target of interest onto the fovea. They can occur reflexively in response to newly appearing targets or voluntarily as part of a specific behaviour such as when an object is being searched for, or related to a memory of an object being present. In a laboratory setting they can be elicited to commands so that a subject can be asked to make a reflexive saccade towards a target or a saccade away from a target, referred to as an antisaccade.

The velocity of large saccades can exceed 500º/s although duration is less than 100ms (Garbutt *et al.*, 2003a). During voluntary saccades the delay between target onset and saccadic initiation is approximately 200ms. Figure 1.2 shows a schematic representation of the neural command used to generate a saccade, known as the pulse-step signal. The “pulse” is the eye velocity command that overcomes the natural resisting forces created by the orbital supporting tissues. The second stage, termed the “step”, is the eye position command that holds the eye in position counteracting orbital elasticity.

Figure 1.2. *Saccadic and antisaccadic eye movements being made to a 10° target jump. The bottom panel shows a schematic representation of the pulse-step command (vertical lines showing the occurrence of neural activity at the ocular motor neuron) to initiate and maintain the saccadic eye movement. The "pulse", is the eye velocity command that overcomes the natural resisting forces created by the orbital supporting tissues. The second stage, termed the "step", is the eye position command that holds the eye in position counteracting orbital elasticity.*



1.2.1.1. Saccadic measurements

When looking at the characteristics, frequently used measures are the peak velocity and the duration of the saccade. These are often plotted as a function of the amplitude. A definite relationship has been described between the amplitude and peak velocity of saccades called the main sequence in which there is a well defined linear relationship between amplitude and peak velocity of saccades less than 20º in amplitude (Boghen *et al.*, 1974; Bahill & Stark, 1975).

1.2.1.2. Saccadic impairments

The accuracy of saccades is usually measured by examining the gain of the response (saccadic amplitude / target amplitude). Disorders of the saccadic system can include those that affect saccadic velocity, such as myasthenia gravis and those that interrupt saccades such as restrictions in the orbit (Oohira *et al.*, 1986; Barton *et al.*, 1995). Ocular motor nerve palsies (CN III, CN IV, CNVI) have shown adaptive changes in saccadic amplitude (Kommerell *et al.*, 1976). Deterioration of saccadic accuracy can be manifest in cerebellar disorders (Kimmig *et al.*, 2002). Disorders of the basal ganglia such as Parkinson's or Huntington's disease can result in impaired saccadic initiation (Lasker & Zee, 1997).

1.2.2. Smooth Pursuit

The smooth pursuit system enables us to maintain constant foveal vision when tracking a single continuously moving target. Normally, a stimulus is required for smooth pursuit initiation such as a target movement across the retina, in particular the foveal or

parafoveal region. Figure 1.3 shows a schematic illustration of smooth pursuit eye movements, depicting the eye smoothly tracking the target. The response can occur to stimuli moving in the horizontal or vertical directions or a combination of the two meridians in an oblique direction. It has been shown for the horizontal axis that pursuit is better for target motion towards the fovea compared to targets moving away from the fovea (Tychsen & Lisberger, 1986; Carl & Gellman, 1987). For vertical smooth pursuit the response is superior for targets moving in the lower visual field compared to the upper visual field (Tychsen & Lisberger, 1986; Hutton & Tegally, 2005). Brighter targets, increased attention and larger stimuli have been shown to result in better smooth pursuit (van den Berg & Collewijn, 1986; Hutton & Tegally, 2005). Overall, tracking targets in the horizontal dimension is superior to the vertical direction (Baloh *et al.*, 1988; Rottach *et al.*, 1996).

1.2.2.1. Smooth pursuit measurements

Properties of the smooth pursuit response that are commonly measured are related to commencing and sustaining the response. To measure the onset of the response, a procedure was developed by Rashbass (1961) and Robinson (1965) referred to as the *step–ramp* paradigm as shown in Figure 1.3. Label 1 shows a static target displayed for the subject to fixate. Label 2 on Figure 1.3 shows the target then making a rapid shift, the *step*, to one side of the fovea. From here the target makes a smooth movement in the *opposite* direction, known as the *ramp* indicated by label 3. The eye movement in response to the step- ramp paradigm usually demonstrates the eyes making a smooth movement in the direction of the ramp with *no saccade* made towards the step. This is depicted by label 4

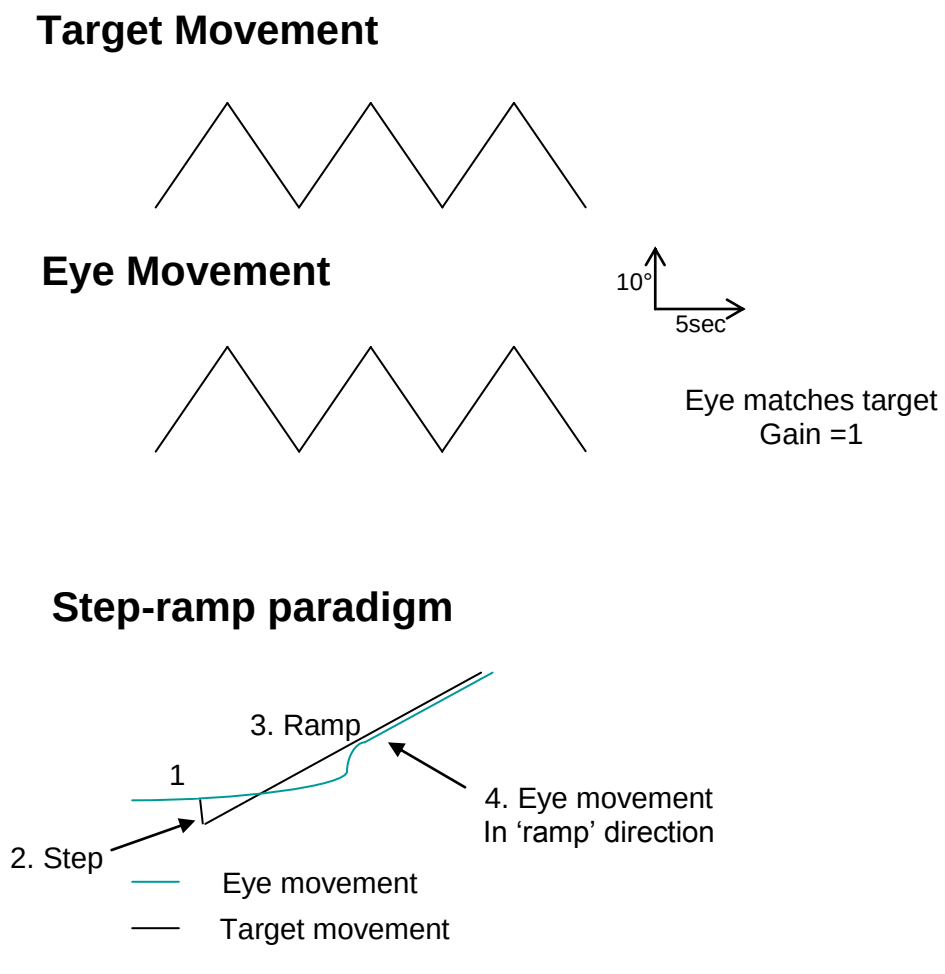
on Figure 1.3. It is from this behaviour that the onset of the smooth pursuit eye movement can be analysed.

A measure of how well the subject sustains the response is given by the gain (eye velocity / stimulus velocity). For normal subjects, this is usually very close to 1 (i.e. target velocity equals eye velocity) up to a stimulus velocity of 100º/s (Meyer *et al.*, 1985).

1.2.2.2. Smooth pursuit impairments

Impaired smooth pursuit can result from cerebral lesions in the posterior hemisphere which lead to reduced smooth pursuit gain (Troost *et al.*, 1972). Impaired pursuit is often a common finding in many neurological disorders such as Parkinson's disease and motor neurone disease (Das *et al.*, 1995). A reduction in smooth pursuit gain has been documented with increasing age, with gains in young and middle aged subjects (mean age 42 years) found to be better than elderly subjects (mean age 65 years). In particular, reduced gain has been found to occur at low target velocities due to a reduction in steady state gain and at high velocities due to acceleration saturation at these velocities (Spooner *et al.*, 1980; Zackon & Sharpe, 1987; Paige, 1994).

Figure 1.3. *Smooth pursuit eye movements showing the eye smoothly tracking the target. The bottom panel shows the step-ramp paradigm commonly used to analyse the onset of the smooth pursuit response. Label 1 shows a static target displayed for the subject to fixate. Label 2 shows the target then making a rapid shift, the step, to one side of the fovea. From here the target* makes a smooth *movement in the opposite direction, known as the ramp indicated by label 3. The eye movement in response to the step-ramp paradigm usually demonstrates the eyes making a smooth movement in the direction of the ramp with no saccade made towards the step depicted by label 4.*



1.2.3. Vergence

The ocular motor systems referred to above move the eyes in a conjugate manner to maintain foveal fixation. Vergence eye movements serve to direct the eyes to the object of interest by moving the eyes in a disconjugate manner to maintain binocular fixation at changing distances. Maddox (1893) identified two main factors that drive our vergence system, namely image disparity and image blur.

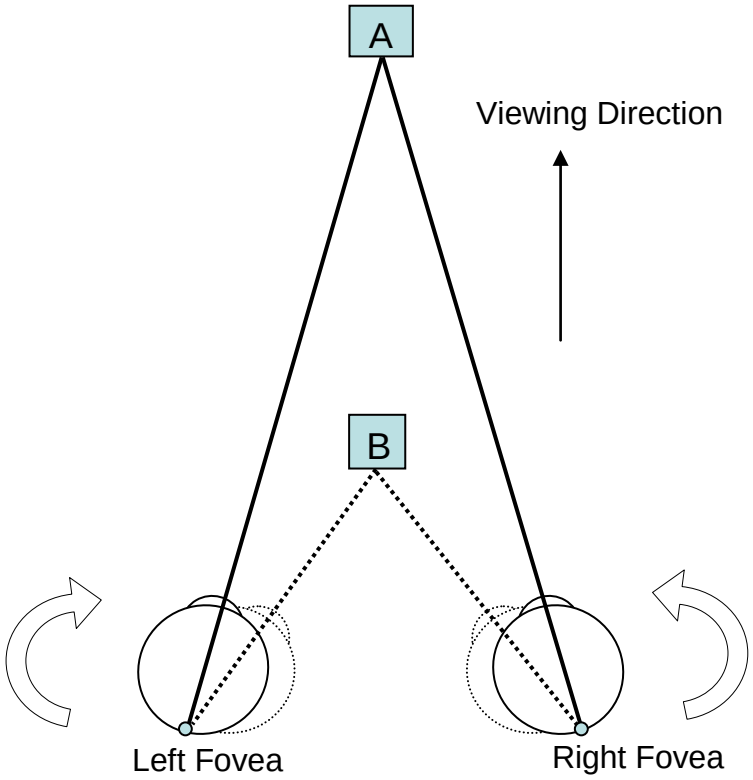
Image disparity results from images falling on non corresponding retinal points. These stimulate our fusional vergence system that moves the eyes enabling us to see a single image. Figure 1.4 shows an example of horizontal vergence eye movements. A convergence movement is required to move fixation from target A to target B and a divergence movement to move fixation from target B to target A.

Image blur results in accommodative vergence enabling us to see a clear image. The process of accommodation results from the refractive power of the lens in the eye changing due to contraction of the surrounding cilliary muscle. This is accompanied by convergence of the eyes and constriction of the pupil. As this process includes three key components that connect both disparity and blur driven systems, it is often referred to as the "near triad" (Semmlow *et al.*, 1986).

1.2.3.1. Vergence Measurements

Fusional vergences are measured in prism dioptres ($^{\Delta}$). One prism dioptre represents the strength of prism that deviates a light ray by 1cm measured at 1 metre, which equates to approximately 0.5 degrees. The horizontal vergence system, which encompasses convergence and divergence of the eyes, is the most flexible system.

Figure 1.4. *Diagram to show an example of horizontal vergence eye movements, for the eyes to maintain binocular foveal fixation from object A to B, the eyes must converge. Conversely to return back to object A, a divergence movement must be made.*



The normal horizontal fusional amplitudes for convergence are 35-40$^{\Delta}$ at near (33 cms) and 15$^{\Delta}$ at distance (6 metres) and for divergence are 15$^{\Delta}$ at near and 5-7$^{\Delta}$ at distance. Although we are able to make vertical and torsional vergence movements, the normal range for vertical and torsional directions is about 6$^{\Delta}$ (3°) and 6º respectively, hence much smaller compared to the horizontal vergence system (Mein & Harcourt, 1986).

1.2.3.2. Development of vergence responses

In the new born, any misalignment of the eyes *normally* resolves in the first two months of life (Horwood, 2003) and it has been demonstrated that at three months infants are able to make vergence movements. The vergence system is said to be fully developed at eight years and demonstrates no significant change up to 40 years of age beyond which some deterioration has been noted in the normal population (Qing & Kapoula, 2004).

1.2.3.3. Vergence impairment

Since the vergence system is crucial in maintaining ocular alignment (Howard & Rogers, 2002) , any disorder of this system can lead to ocular misalignment known as strabismus (Von Noorden & Campos, 2001). If the eyes are misaligned in the horizontal direction, this is referred to as esotropia (nasal) or exotropia (temporal), in the vertical direction as hyper / hypotropia, and in the torsional direction as incyclotropia and excyclotropia. Early onset strabismus from birth or during childhood (usually less than 8 years of age) could result in visual suppression of the affected eye causing *amblyopia* (Von Noorden, 1977). Later onset of strabismus after the development of binocular single vision, results in double vision (Von Noorden, 1990b). Other conditions such as Parkinson's disease have been shown to be associated with impairment in the vergence system (Repka *et al.*, 1996).

1.2.4. The Vestibular System

The peripheral vestibular system comprises of the *labyrinth* that lies within the petrous temporal bone. It contains the *cristae* of the *semicircular canals* and the *maculae*

of the *otolith* organs: the *utricle* and *saccule*. Both structures contain hair cells that provide neural impulses to the vestibular system. The semicircular canals sense head rotations and the otolith organs sense linear motion (translations) and static tilt of the head (Leigh & Zee, 2006, p25).

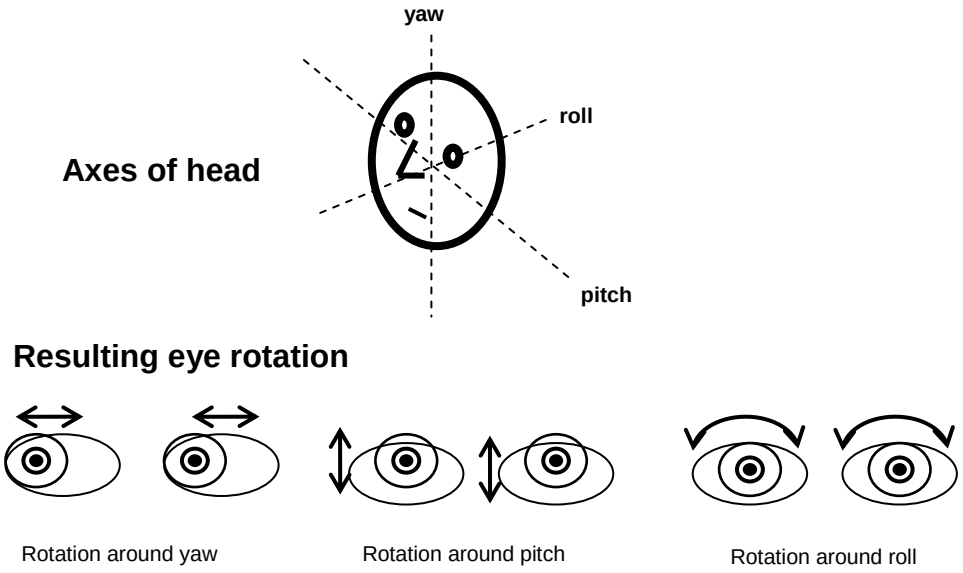
The vestibular system, in combination with the smooth pursuit and optokinetic system, generates compensatory eye movements during brief head movements. These eye movements are referred to as the vestibulo-ocular reflex (VOR). The rotational VOR compensates for rotational head movements in space and receives its input from the semicircular canals. Figure 1.5 shows the axes of rotation in which head movements are defined. These are referred to as yaw, pitch and roll axes, where the rotational VOR moves the eyes in the opposite direction to head movement in horizontal, vertical and torsional directions, respectively.

The *translational* VOR compensates for movements of the head and body such as occurs when standing on a moving side walk (Manali, 2006). This system responds to linear head movements described as heave *(side to side)*, bob *(up and down)* and surge *(anterior and posterior)* movements. This in turn produces compensatory horizontal, vertical and vergence eye movements, respectively, driven by the otolith organs. Both systems produce eye movements at a short latency during high frequency head movement. Rotational head movements of frequency 0.5-5.0 cycles/second have a latency of 7-15ms and a gain (eye velocity / head velocity) close to one (Leigh & Zee, 2006).

For translational movements and horizontal and vertical rotations, the VOR must be adjusted according to the distance of fixation in order to maintain the images on the fovea. This results in the amplitude of the VOR increasing at near viewing. Head rotations

in the *roll* axes displace images from fovea much less and so no changes in the torsional VOR demands are required from viewing near to distance viewing (Leigh & Zee, 2006).

Figure 1.5. *The rotational vestibulo-ocular reflex (VOR). The axes of rotation in which head movements are defined are referred to as yaw, pitch and roll axes, where the rotational VOR moves the eyes in the opposite direction to head movement in horizontal, vertical and torsional directions, respectively.*



1.2.4.1. VOR Measurement

The VOR system is tested by assessing factors that influence the *balance*, *gain* and *phase* of the response (Leigh & Zee, 2006). Vestibular eye movements can be assessed statically by inspecting the eyes with the head still and disrupting fixation using *Frenzel* goggles. Stability of gaze can be noted to see whether there are any spontaneous oscillations and the form of any nystagmus present can be recorded. Dynamic testing can

be achieved using movements of the head and eyes to investigate vestibular imbalance (Leigh & Zee, 2006). For example, VOR impairment can be tested by the subject reading a vision chart comparing acuity with head still to shaking the head at approximately 2Hz. A reduction in VOR gain during this test manifests as a reduction in visual acuity while the head is shaking. To objectively measure gain with quantitative measurements, eye movement recordings can be taken in response to a sudden head rotation, typically 50°/s or 100°/s, and the peak eye velocity measured (Leigh & Zee, 2006, p517).

The phase of the response reflects the timing relationship between the head movement and the eye movement. Normally, this is at 180° as the eyes and the head move at the same velocity in opposite directions.

1.2.4.2. VOR impairment

Disorders of the VOR can be revealed as defects in gain, phase and balance of the response. Clinically, this may cause nystagmus in a specific plane resulting in motion of the visual environment, oscillopsia, and / or reduction in visual acuity. A decrease in VOR gain occurs with age which is primarily the result of a *phase lead* with the reflexive eye movement exceeding the head movement. This has been shown to occur at low and modest frequencies with low and high head velocities, respectively (Peterka *et al.*, 1990a, b; Paige, 1992; Baloh *et al.*, 1993; Baloh *et al.*, 2001). A higher gain in rotational VOR has been reported in children aged between 3-6 years compared to adults aged 21-29 years (Sakaguchi *et al.*, 1997).

1.2.5. Optokinetic Nystagmus (OKN)

The optokinetic system (OKN) is a reflexive ocular motor system that responds to sustained image motion of the visual field. It consists of a slow phase following movement in the direction of image movement, followed by a quick resetting movement in the opposite direction. Figure 1.6 shows a diagrammatic representation of the ocular movement recordings seen during OKN movements. It shows a combination of repetitive compensatory movements displaying a distinctive 'saw tooth' appearance (see ***Movie A*** in *additional addenda* CD showing the OKN response).

Purkinje (1823) was first to describe OKN while watching a cavalry parade (Grusser, 1984). The OKN system also works in combination with the smooth pursuit system and the vestibular system to stabilize the image of stationary targets during head rotations.

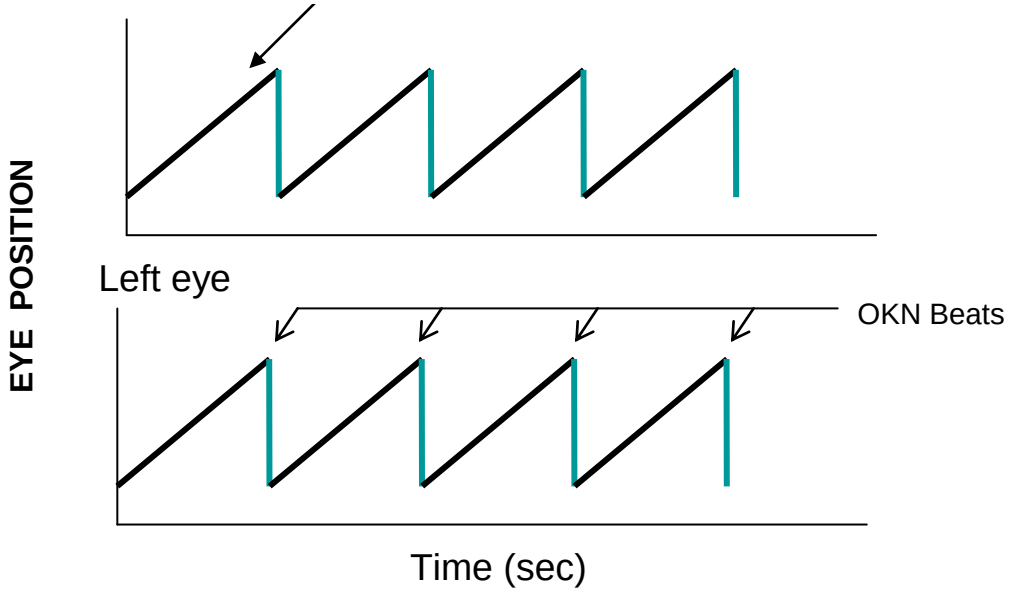
1.2.5.1. OKN Measurement

The parameters used to assess the OKN response are the slow phase gain (SP), beat frequency and amplitude. By assessing the slow phase in relation to the stimulus velocity a measurement of gain can be determined using the following equation

$$\text{Gain} = \frac{\text{slow phase velocity (°/s)}}{\text{stimulus velocity (°/s)}}$$

If eye velocity precisely equals stimulus velocity the gain is equal to one.

Figure 1.6. *A typical optokinetic nystagmus waveform showing a 'saw tooth' appearance. Eye position is depicted of the right and left eye demonstrating conjugate eye movements. The slow phase of the response is shown in black and the fast phase in blue.*



Slow phase: movement in the same direction as target

Fast phase: movement in opposite direction as target

Beat frequency (BF), measured in beats per second (Hz), is determined by the frequency of occurence of the quick phase of the response (Garbutt & Harris, 1999) and is given by:

$$BF(Hz) = \frac{\text{Beats during n seconds stimulation}}{\text{n seconds}}$$

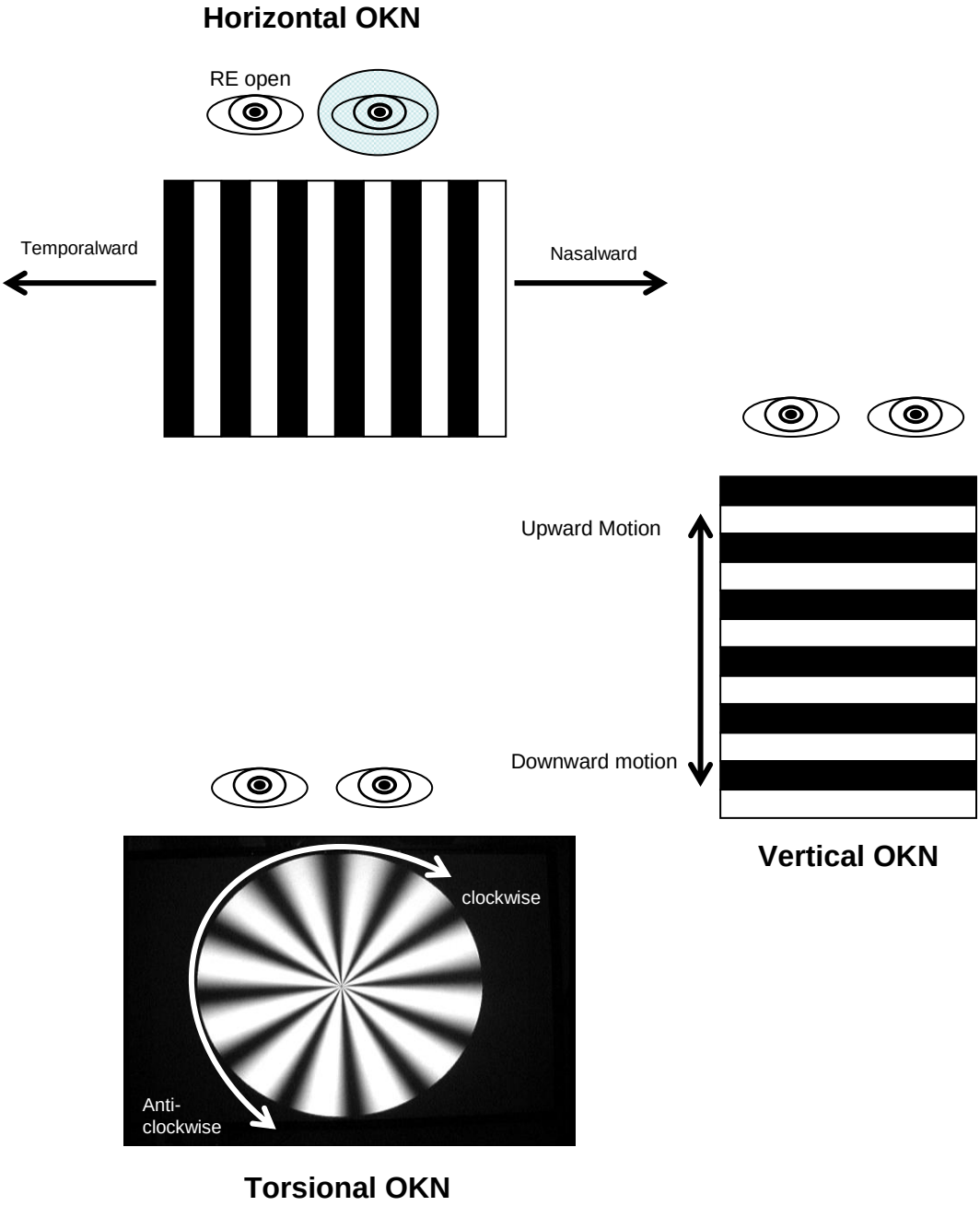
The amplitude (*A*) of the response is described for the size of the slow phase calculated by:

$$A\,(°) = \text{Eye position at end of slow phase} - \textit{eye}\text{ position at end of previous fast phase}$$

The OKN response occurs in healthy individuals for stimuli rotating in the horizontal (right or left), vertical (up or down) and torsional (clockwise or anticlockwise) directions. Clinically, the horizontal and vertical responses have traditionally been tested using an OKN drum or a strip of cloth which consisting of black and white striped stimuli. Horizontal stripes are moved vertically to induce vertical OKN and vertical stripes are moved in the horizontal direction to elicit horizontal OKN. Optokinetic after-nystagmus **(OKAN)** occurs when the initial stimulus that elicits the OKN response stops. It is manifest as a persistence of the OKN eye movement in the opposite direction with a declining velocity of the slow phase (Leigh & Zee, 2006, p52).

As OKN is very difficult to suppress, an absence of OKN can sometimes imply poor vision (Garbutt & Harris, 1999). Currently, there are no tools to assess torsional OKN in a clinical setting. In the laboratory setting the size, speed, direction and type of stimulus can be easily controlled to elicit all forms of OKN. Figure 1.7 shows examples of the various grating patterns that are typically used to elicit optokinetic nystagmus in horizontal, vertical and torsional meridians (see also ***Movie B and C*** *in additional addenda CD for examples of actual Horizontal and torsional OKN stimuli).*

Figure 1.7. *Examples of stimuli used to elicit optokinetic nystagmus in the horizontal (nasalward and temporalward), vertical (up and down), and torsional (clockwise amd anticlockwise) directions. For horizontal OKN stimulation, nasalward and temporalward motion is defined in relation to the fixating right eye. The left eye is occluded (shaded in green).*



1.2.5.2. Horizontal Optokinetic Nystagmus (hOKN)

Two components have been described in the generation of hOKN slow phase responses:

(i) The early OKN component results in a rapid build of the slow phase velocity so that it approximates to the stimulus velocity in 0.5 seconds of its onset displaying prompt optokinetic nystagmus (Abadi *et al.*, 1994). This response is similar to the generation of smooth pursuit and it is this component of the response that is responsible for the fast decline of SPV after stimulation (Fuchs, 1993).

(ii) The delayed OKN component is a slower response where the slow phase velocity gradually builds up and also declines at a slower rate after stimulation (Garbutt & Harris, 1999). This slow decline results in optokinetic after-nystagmus (OKAN). Since OKAN is a purely related to the delayed OKN response, it can be studied to assess any abnormalities of the OKN system without the influence the early OKN system (Garbutt & Harris, 1999).

TerBraak (1936) identified two types of OKN depending on the instructions given to the subject when viewing a stimulus. Figure 1.7 illustrates these two types of OKN movement.

(i) If the subject is asked to actively follow a single detail of the stimulus ‘look’ OKN is generated. The resulting eye movements have a high gain, large amplitude slow phase velocity with a small number of quick phases.

(ii) If, however, the subject is asked to passively look at the stimulus without fixating on certain features then 'stare' OKN ensues. Stare OKN typically has low gain, low amplitude and frequent quick phases (Honrubia *et al.*, 1968).

1.2.5.2.1 Horizontal OKN (hOKN) symmetry

The symmetry of the hOKN response during monocular stimulation is an important parameter. In adult humans, motion of images towards the subject from the periphery (nasalward) and away from the subject to the periphery (temporalward) elicit the same magnitude of OKN (Schor & Levi, 1980; Howard, 1997). However, in young infants there is a weaker response for temporalward motion compared to nasalward motion (Atkinson, 1979; Atkinson & Braddick, 1981; Naegele & Held, 1982; Valmaggia *et al.*, 2004). It is generally agreed that the age at which the response becomes symmetrical is approximately 3- 5 months of age (Atkinson, 1979; Atkinson & Braddick, 1981; Naegele & Held, 1982). However, a recent report found that the response became symmetrical later at 11 months of age in all subjects (Valmaggia *et al.*, 2004). Other factors such as the speed of the stimulus have also been shown to influence the presence of an asymmetry with higher stimulus velocities eliciting a more asymmetric response (Roy *et al.*, 1989; Harris *et al.*, 1994).

Original theories regarding the cause of the asymmetry during the development of hOKN are based on work done in cats in which a similar nasalward asymmetry is observed (Atkinson, 1979). It was postulated from this work that the temporalward response is primarily modulated by a cortical pathway, which develops at a slower rate than the subcortical pathway present at birth which mainly controls the nasalward response. This

theory however cannot be applied to human infants because there is evidence of a fast build up of slow phase OKN velocity from one month of age indicative of the *early* **cortical** OKN response operating at this time (Hainline *et al.*, 1984; Harris *et al.*, 1994). An alternative explanation regarding the cause of asymmetry being related to the pathways leading from the retina to the cortex has been given. It has been suggested that pathways for nasalward motion mature earlier than those responsible for temporalward motion (Atkinson & Braddick, 1981; Harris *et al.*, 1996). The development of the temporalward response has also been said to coincide with the development of smooth pursuit eye movements (Jacobs *et al.*, 1997).

1.2.5.3. Vertical Optokinetic Nystagmus (vOKN)

Vertical OKN has been less thoroughly studied than hOKN. Garbutt *et al.* (2003) have compared the fast phase of the vOKN response to vertical saccades of less than 10° amplitude (Garbutt *et al.*, 2003a). Although the voluntary saccades were slightly faster than quick phases of vOKN, both types of vertical eye movement were found to have similar amplitude-peak velocity and amplitude-duration relationships. This allowed the authors to conclude that vOKN testing could be used as an alternative way to look at vertical saccades.

Optokinetic after-nystagmus (OKAN) in the vertical direction has been described to be sometimes present for upward stimulation only (Matsuo & Cohen, 1984; Murasugi & Howard, 1989a; Bohmer & Baloh, 1990) although it is commonly not present in any vertical direction at all.

1.2.5.3.1. Vertical (OKN) symmetry

The little literature describing vOKN responses during early infancy suggests that, similar to the hOKN response, there appears to be an asymmetry in the direction of response. Hainline *et al.* (1984) reported reduced response to *downward* vOKN in early infancy. In contrast to the hOKN response that consistently shows the eventual development of a symmetrical response in the normal population, there appears to be greater disagreement in the literature regarding vOKN asymmetry. Hainline *et al*. (1984) suggest that the initially reduced *downwards* vOKN response becomes equal to the response for *upward* moving stimuli at approximately four months of age However, the majority of studies in the development of the response into adulthood show disagreement with this. Most literature describes vertical OKN to be greater for stimuli moving in the *upward* direction in normal adults indicating the persistence of this asymmetry from birth (Matsuo & Cohen, 1984; van den Berg & Collewijn, 1988; Murasugi & Howard, 1989a; Bohmer & Baloh, 1990; Ogino *et al.*, 1996; Garbutt *et al.*, 2003a; Garbutt *et al.*, 2003b). Garbutt *et al.*,(2003b) reported the slow phase gain of the vOKN response to have a greater response for *upward* moving stimuli, however some subjects did show a *symmetrical* response.

The asymmetry of the normal vOKN response in infants has been attributed to the lack of interaction between both hemispheres (Hainline *et al.*, 1984). This is because an exaggerated form of vOKN asymmetry was noted in monkeys after the optic chiasm, corpus callosum and other interhemispheric structures were sectioned (Pasik *et al.*, 1971).

1.3. Torsional eye movements

1.3.1. Historical review

When referring to horizontal and vertical movements of the eyes, von Helmholtz (1910) wrote,

"*The only movements that can possibly be executed are rotations or movements by which one side of the eyeball enters the ocular cavity, while another side emerges from it."*

When describing the third dimension of eye movement, he wrote,

"… the eye ball might still be able to turn anyway whatever around the line of fixation axis…such rotations of the eyeball around the line of fixation are generally called torsional- rotations (Raddrehungen (or rollings)), because in this case the iris rolls around like a wheel (ein Rad) (Helmholtz & Southall, 2000)."

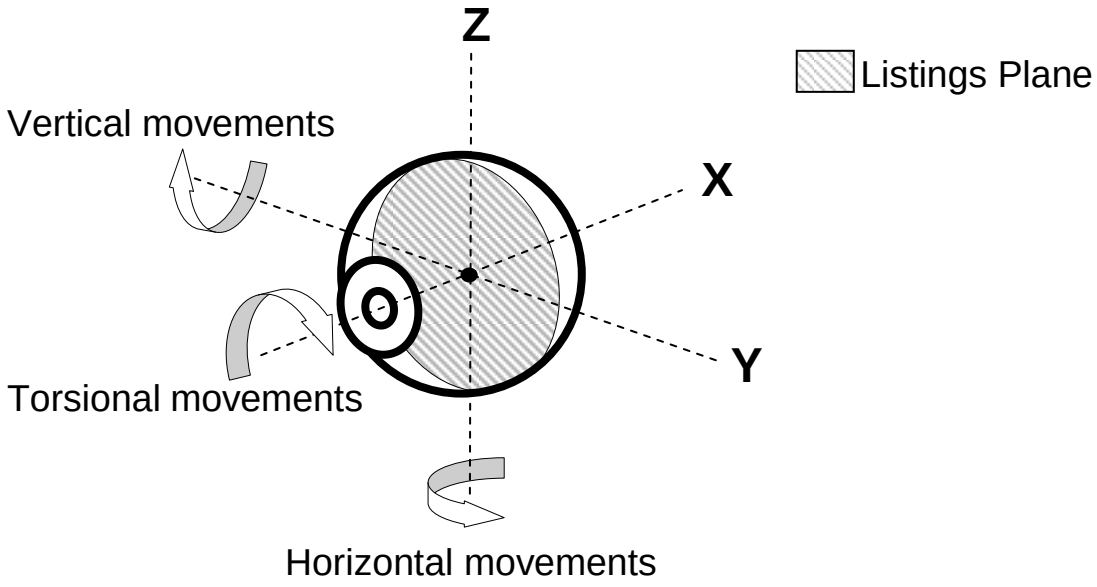
Figure 1.8 shows all three axes of eye rotation. Torsional eye movements occur when the eyes rotate around the X-axis resulting in extorsion and intorsion eye movements.

Listing, a 19th century physiologist, was first to observe that torsional rotations of the eyes were coupled with both horizontal and vertical eye movements in humans. This lead to the description of *Listing's law* reported by von Helmholtz in 1867 (Helmholtz & Southall, 1962). This law states that there is a unique eye position from which any normal eye direction can be reached by rotation around a singular axis known as Listing's plane. Listing's plane is orientated perpendicular to our normal primary direction of viewing (Haslwanter, 1995; Wong, 2004).

A consequence of this law is that when the eyes move to tertiary gaze positions, i.e. combined horizontal and vertical eye positions, then a tilting of the vertical meridian of the

eye occurs. In addition to Listing, Donders (1848) stated that the amount of torsional movement of the eye is fixed for a given horizontal and vertical position. We know that most forms of saccadic and smooth pursuit eye movements follow Listing's and Donders' laws (Ferman *et al.*, 1987b, a; Straumann *et al.*, 1996).

Fig 1.8. *Diagrammatic representation of the three axes of eye rotation known as 'Ficks' axes. Rotation around the X axis results in torsional eye movement in the intorsion (towards the nose) or extorsion (away from the nose) directions. Listing's plane is perpendicular to this axis.*



1.3.2. Importance of torsional eye movements

Torsional eye movement control stabilizes retinal images and maintains correspondence of these images between both eyes. Impairments in normal torsional eye control allow us to appreciate the importance of torsional eye stability required in our ocular motor system. For example, thyroid eye disease which results from an immune

reaction on orbital fibroblasts causes an increase in muscle tissue volume altering orbital muscle mechanics (Bahn & Heufelder, 1993). This results in large amounts of torsional disparity between the eyes causing torsional diplopia which is very difficult to manage clinically. Also, torsional muscle imbalance as a result of denervation of the trochlear nerve results in excessive extorsion. This is as a result of the unopposed action of the antagonistic muscle, sending the eyes out of equilibrium in the torsional meridian (Leigh & Zee, 2006, p423).

Furthermore, a torsional eye movement abnormality can be an indicator of pathological processes occurring in the brain. Acquired spontaneous torsional oscillations (nystagmus) can be indicative of a medullary lesion or multiple sclerosis (Lopez *et al.*, 1992). When correlating oculomotor features to MRI images of the brainstem of 27 patients with acquired nystagmus, it was found that torsional nystagmus was most commonly associated with medullary lesions (Lopez *et al.*, 1995). Eye movement recordings of three patients with episodic ocular torsion due to mid brain lesions have shown the fast component of the torsional oscillation rotates the eyes towards the side of the lesion. The occurrence of bilateral spontaneous torsional eye movements in brainstem lesions has been attributed to functional asymmetry in vestibular pathways responsible for slow phase compensatory eye movements used during head tilt (Bentley *et al.*, 1998).

There are also clearly identified components of congenital abnormalities such as dissociated vertical deviation (DVD) associated with essential infantile esotropia syndrome (Van Rijn *et al.*, 1997) and congenital forms of nystagmus (Averbuch-Heller *et al.*, 2002) that have specific torsional components. Unlike rotations in the horizontal and vertical meridian, primary torsional eye movements (not associated with the other

movement of the eyes from the primary position) have none or very limited (if any) voluntary control (Thilo *et al.*, 1999). This is probably why pathological processes in the torsional meridian are sometimes more difficult to treat (Mein & Harcourt, 1986).

1.3.3. The role of torsional eye movements in vision perception and binocularity

1.3.3.1. Cyclofusion

The ability to perform torsional eye movements with the aim of maintaining binocular vision is referred to as cyclofusion (Lazenby, 2000). The eye movement made to achieve cyclofusion is referred to as cyclovergence (British Orthoptic Society, 2001). When a disparity of images occurs in the torsional meridian it is assumed, just as with horizontal and vertical disparate images that an ocular motor response occurs to maintain binocular vision. The purpose of cyclovergence is to keep the images of the key horizontal components of the visual field in orientational alignment. This is so that residual disparities in the vertical components of the image can be used to assess the slant of objects (Howard *et al.*, 1994). Presently, there is ongoing debate as to whether cyclofusion is a purely motor or a sensory adaptation or a combination of the two (Lazenby, 2000).

1.3.3.2. Sensory cyclofusion

Kertesz & Jones (1970) have demonstrated that no cyclofusional movement takes place when stimuli are presented with a cyclo disparity, resulting in a sensory fusion of about 10° in amplitude. This is in agreement with other studies that have also

demonstrated no motor component to the cyclofusional response (Jampel *et al.*, 1976; Mikaelian *et al.*, 1990). It has been suggested that there are central nervous system mechanisms that are responsible for the fusion of disparate images in the torsional meridian. This has also been used to explain the interpretation of spatial relationships when the head or body is tilted.

1.3.3.3. Motor cyclofusion (cyclovergence)

In contrast to these findings Guyton (1988) has stated that the cyclofusion response can also include up to approximately 6-8° of motor cyclofusinon in addition to approximately 8° of sensory fusion. Motor fusion has been said to occur due to a large field stimulus disparity and sensory cyclofusion due to large Panums's areas. Horizontal lines have been shown to be more effective in evoking a motor cyclofusional response. Furthermore a picture with highly significant contours is better still than horizontal and vertical lines (Crone & Everhard-Hard, 1975; Crone & Everhard-Halm, 1976). Sullivan & Kertesz (1979) used circular disks with randomly segmented horizontal lines ranging from 10° to 50° in diameter and measured eye movements using the scleral search coil. They found that the motor cyclofusion response compensated for approximately 49-80% of the torsional disparity, the remainder being compensated for by non-motor mechanisms.

1.3.3.4. Effect of stimulus area

Howard *et al*. (1994) used a Wheatstone stereoscope to investigate the effects of stimulus area and the gain of the cyclovergence response. The gain of the cyclovergence response was found to increase with increase in stimulus field size. A significant

difference was found between the smallest stimulus diameter of 5° and 20° compared to the gain evoked to the largest field size of 75°. Interestingly, the cyclovergence response was unaffected when an annular stimulus (i.e. with the central portion missing was used). This enabled the authors to conclude that cyclo disparities in the peripheral visual field were crucial in eliciting cyclovergence because within the central visual field greater information is received regarding the inclination of surfaces.

1.3.3.5. Perceptual compensation for torsion

Studies investigating the perceptual compensation of torsion are based on an individual's ability to perceive an object as vertical or the recognition of *slant* of an object during head and/or body tilt. The slant and location of an object can be represented relative to the head if the position of the eyes in the orbit is available and combined with retinal coordinates (Poljac *et al.*, 2005). Haustein (1992) found that individuals were able to align points relative to the mid sagittal plane of the head with only a small error. This was inspite of the eye movement when the head was tilted giving a bigger error. This indicated, other perceptual mechanisms probably being used to complete the task. Poljac *et al.* (2005) investigated compensation for eye torsion when the plane of regard is identified. Subjects were asked to judge the elevation of a flashed probe while fixating straight ahead, at secondary and tertiary positions of gaze, and while fixating binocularly and monocularly. Induced ocular torsion did not cause any change of the perception of the plane of regard for both monocular and binocular conditions. The authors postulated that there is a mechanism that integrates the retinal representation and the eye orientation signal to

compensate for torsion. This is in agreement with previous authors (Haustein & Mittelstaedt, 1990; Haustein, 1992).

1.3.4. Ocular counter roll

A head tilt towards the shoulder induces ocular counter roll (OCR). Torsional eye movements are elicited in the opposite direction to head tilt. The OCR is induced by the vestibular system; in particular the otolith organs as they continually sense the head position with respect to gravity while semicircular canals respond to the movement (Petrov & Zenkin, 1973). Counter rolling of the eyes compensates for approximately 10% of the head tilt (Collewijn *et al.*, 1985; Averbuch-Heller *et al.*, 1997; Pansell *et al.*, 2005a).

The time constant for the activity in the nerve afferents to the semicircular canal during rotation is short (approximately 5 seconds). Therefore, if the OCR position induced by a head tilt is to be maintained, there must be other mechanisms than those related to the angular velocity from the semicircular canals for this to occur. The utricle has been shown to be main contributor to the OCR during sustained head tilt (Groen *et al.*, 1999).

1.3.4.1. Maintenance of response over time

The maintenance of the magnitude of OCR response over time has recently been investigated. Pansell *et al.* (2005b) examined five male subjects in response to manual head tilts lasting for 10 minutes. In the static tilted position, the torsional eye position was found to change gradually. Initially all subjects demonstrated increased OCR in the opposite direction of the head tilt, lasting 30 seconds without visual spatial cues available, and 55 seconds with spatial cues. The torsional drift then changed direction with the eyes

moving back to the direction ipsilateral to the head roll. The point in time in which the torsional drift shifted direction differed depending whether the visual target had visual spatial cues. After 10 minutes the OCR significantly decreased.

1.3.4.2. Mechanism

The mechanism of the torsional drift back towards the reference position could be due to an adaptation of the utricular receptors (Macadar & Budelli, 1984). A leakage of the neural integrator is another potential explanation for the drift of OCR towards the reference position. Crawford *et al*. (1991) reported that pharmacological inactivation of the interstitial nucleus of Cajal caused impairment of the torsional integrator which supports the theory that counterolling is maintained by the neural integration of the pulse signal rather than a direct tonic vestibular input to motor neurons.

Memory for angular changes in position detected by the semicircular canals could serve as an explanation for the drift back to the reference position. A recent study has shown the existence of such a memory for rolling head movements (Tribukait, 2003). Such a memory for angular changes in position might possibly influence the torsional position of the eyes during prolonged static head tilt. If the semicircular canals sense the change in head position then a "forgetting" of the semicircular canal input would be reflected in a gradual decrease in OCR.

1.3.5. Torsional Optokinetic Nystagmus (tOKN)

Torsional OKN is an ocular motor response occurring when viewing a rotating stimulus. Figure 1.9 depicts Brecher's first description of the response in 1934 when he

observed the conjunctival blood vessels of a subject that viewed a rotating sectored disc through a telescope (Brecher, 1934). Similar to the horizontal and vertical OKN response, he observed that the eyes underwent a rotation of constant amplitude in the same direction of stimulus motion that was interrupted by nystagmic jerks in the opposite direction (Kertesz & Jones, 1969).

Figure 1.9. *The original experimental stimulus used by Brecher to examine torsional optokinetic nystagmus. (Taken from Brecher (1934))*

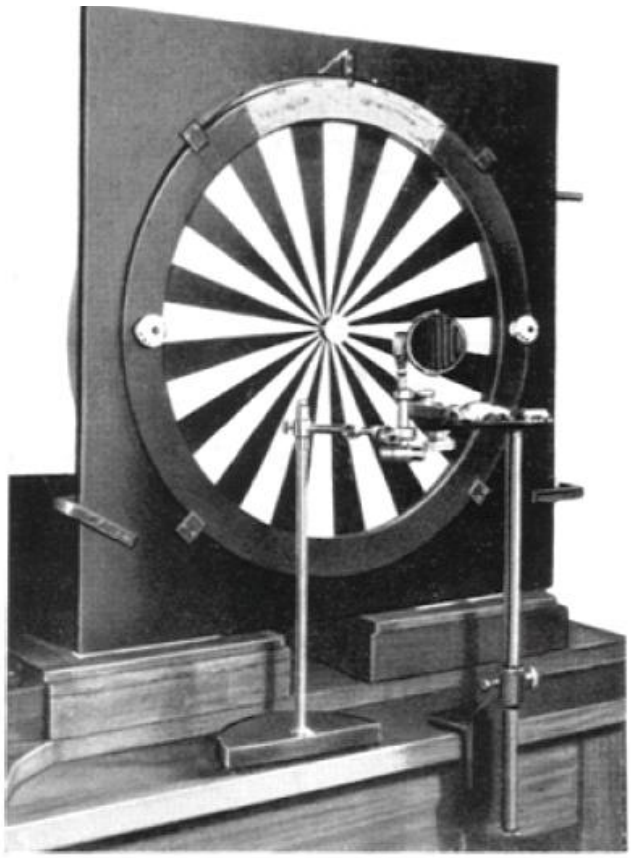


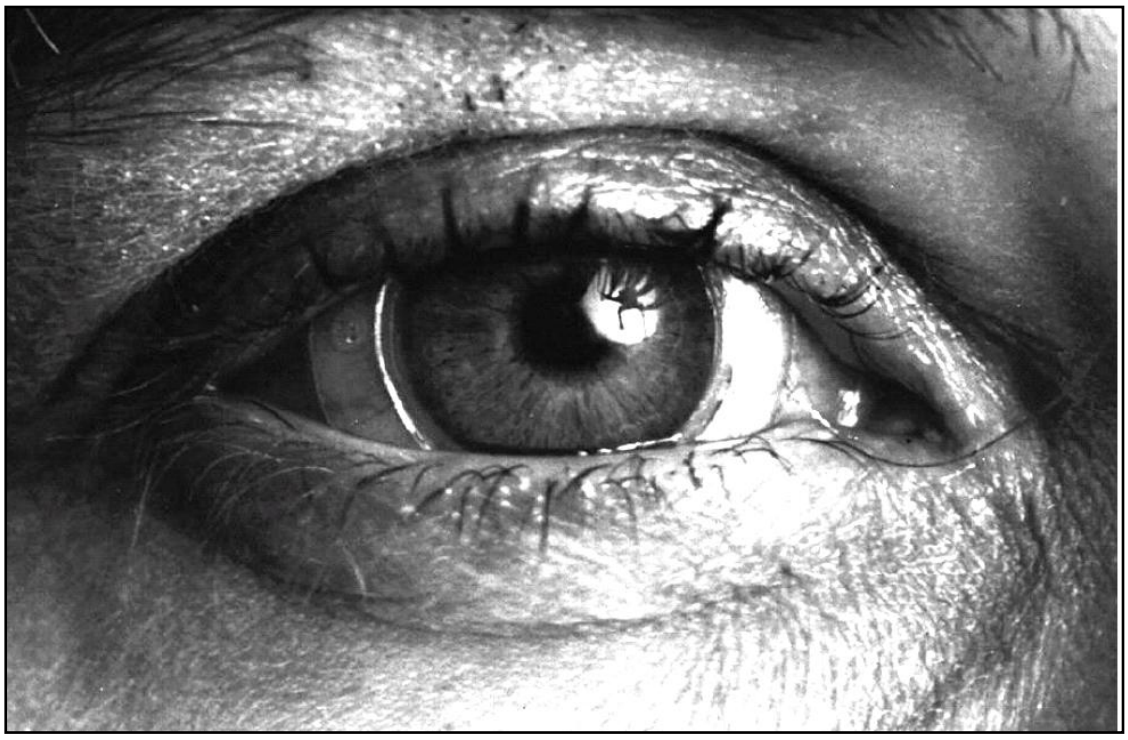
Abb. 3. Versuchsgerät zur Messung der optokinetischen Rollung mittels Fernrohr und Nachbild-Testfaden-Methode.

1.3.5.1. Torsional eye movement recording

There is limited literature regarding the development of the tOKN response with age and its normal properties. This is mainly because torsional eye movements could not

able to be tested continuously until the development of a modification of a recording technique originally pioneered by D.A. Robinson, named the *scleral search coil* (Robinson, 1963). Figure 1.10 displays the scleral search coil as worn on the eye.

Figure 1.10. *The scleral search coil comprises a silicon annulus in which two coils of wire are embedded. One of which measures horizontal and vertical movement and the other torsional eye movements (taken from Leigh and Zee, 2006).*



Initially Robinson used a suction contact lens that was kept in place by a small tube that was connected to a vacuum pump. Within this lens were electrical windings that were either in the same plane of the iris or perpendicular to it. When the subject was placed in an electromagnetic field, the induction current in the windings was proportional to the rotational angle of lens and in turn the eye in the magnetic field. Later, Collewijn *et al.* (1975) created a modification to this technique by replacing the suction contact lens by a

silicon annulus which was more comfortable to wear. This version could only measure horizontal and vertical eye movements and so it was modified to include measurement of eye torsion in 1985 (Collewijn *et al.*, 1985). The advantages and disadvantages of this and other later developed eye movement recording devices are displayed in Table 1.1.

Torsional OKN is usually elicited with a stimulus rotating in front of a subject in the clockwise or anticlockwise directions in the coronal plane (see also ***Movie C, clip 1 and clip 2*** in *additional addenda CD which show a tOKN stimulus*).

Radiating stripes or random dot stimuli are commonly used in generating the response. There are no developmental studies describing the response from birth due to the lack of recording methods to measure eye torsion in infants. The tOKN response has been found to be symmetrical for stimuli rotating in the clockwise and anticlockwise directions in normal individuals (Cheung & Howard, 1991; Suzuki *et al.*, 2000).

1.3.5.2. Torsional OKN properties found in previous literature

1.3.5.2.1. Suppression

The effects of a fixation target during stimulation of a rotating target have been investigated. The tOKN response has been found to be suppressed when a subject is asked to fixate a stationary target superimposed on the tOKN stimulus (Suzuki *et al.*, 2000). This response is similar to that described when a target is fixated during hOKN stimulation (Barnes & Crombie, 1985). However, contrary to the hOKN system, which is said to be suppressed by its pursuit system during fixation, a non pursuit mechanism has been described to suppress the tOKN system during visual fixation (Suzuki *et al.*, 2000).

Table 1.1. *The advantages, disadvantages and ability to measure torsional eye movement of different eye movement recording methods (Adapted from Leigh and Zee, 2006).*

Method	Advantages	Disadvantages	Torsional recordings
Clinical observation (ophthalmoscopy)	Simple No discomfort	No record (difficult to distinguish different oscillations)	Difficult if combined with other rotations
D.C. electro-oculography (EOG)	Non invasive Large range horizontal (± 40°) Can be used in children 1° resolution Inexpensive	Electrical and Electromyographical noise Difficult to measure vertical movements Lid artifact Difficult calibration	No
Infrared differential limbus reflection technique	Non invasive 0.5° resolution	Limited Range: ±20° Horizontally ±10° Vertically	No
Purkinje image tracker (lens and cornea)	Non Invasive 0.5° resolution	Lens motion artifact Bite bar must be used Expensive	No
Video based systems	Non invasive (minimal discomfort) ≤0.5° resolution Noise depends on camera resolution and digitization rate Good vertical recording	Heavy head piece Noise of system may limit analysis Expensive	Yes
Magnetic search coil using scleral annulus	Sensitive to <1 min of arc Large linear range ±180° Unlimited field of view	Invasive technique Expensive Potential for corneal abrasion	Yes

1.3.5.2.2. Head position

In monkeys slow phase velocity has been shown to increase if the head is tilted back (Schiff *et al.*, 1986), however no such changes in tOKN have been observed in humans with changes in head position (Morrow & Sharpe, 1993).

1.3.5.2.3. Torsional OKAN

Similar to vertical OKAN, the torsional OKAN response has been described to be small or absent (Cheung & Howard, 1991). Morrow & Sharpe (1993) described torsional OKAN as being present in only 25% of trials. They also observed that the tOKN response, in contrast to the horizontal OKN response, shows no evidence of the *delayed* OKN as tOKN peak slow velocity occurs within the first few beats of the tOKN response after which slow phase velocity declines. This is in contrast to hOKN generation in which the early OKN dominates in the light, but a delayed OKN system is revealed when looking at OKAN in the dark (Garbutt & Harris, 1999).

1.3.5.2.4. Perceptual effects

Despite the absence of torsional OKAN, a motion after effect when the stimulus stops rotating has been described where illusory motion of the stimulus is described in the *opposite* direction to initial stimulus rotation. Unlike OKAN, in which eye movements occur in the *same* direction before and after stimulation, the motion after-effect was accompanied by eye movements in the opposite direction to what were present during tOKN stimulation (Seidman *et al.*, 1992). Another perceptual change, the sensation of self movement (circular-vection) during viewing a tOKN stimulus has been described. Thilo *et*

al. (1999) reported that this enhances the tOKN response resulting in an increased gain during periods of circular-vection. Cheung & Howard (1991), however, found no such change in the tOKN response.

Before discussing the key areas of investigation in this thesis in relation to torsional optokinetic nystagmus, an overview of the neurophysiological aspects of eye movement control will now be described.

1.4. Neurophysiology of eye movements

1.4.1. Cortical and subcortical control

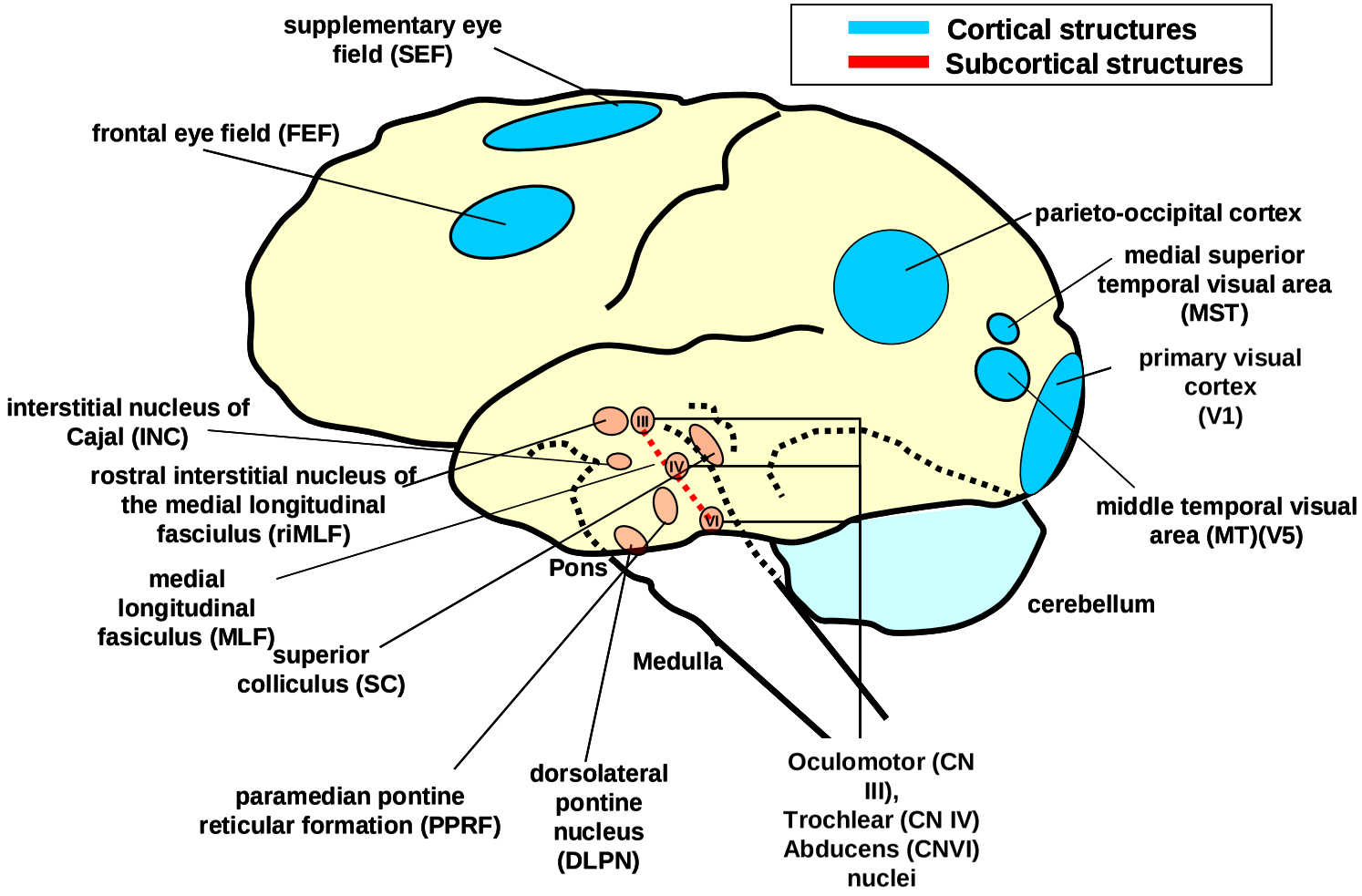
The key cortical structures involved in eye movement control are the primary visual cortex (V1), middle temporal visual area (MT or area V5) and medial superior temporal visual area (MST), parieto occipital cortex, the frontal eye fields (FEF) and the supplementary eye fields (SEF). These structures have important roles particularly in the generation of saccadic and pursuit movements (Ansons *et al.*, 2000). Figure 1.11 highlights the cortical areas (in blue) and subcortical areas (in red) of the brain used for generating eye movements.

Subcortical structures involved in saccadic control include the superior colliculus (SC), pontine paramedian reticular formation (PPRF), the medial longitudinal fasiculus (MLF) and the rostral interstitial nucleus of the medial longitudinal fasciculus (riMLF). Subcortical pursuit eye movements arise from the dorsolateral pontine nuclei (DLPN) and cerebellum. The neural integrators responsible for stable gaze holding are located in the cerebellum, medulla (vestibular nuclei) and the interstitial nucleus of Cajal (INC).

1.4.2. Neural pathways for optokinetic nystagmus

Figure 1.12 illustrates the basic neural pathways for horizontal OKN generation. Visual information from moving stimuli is encoded in the ganglion cells of the retina. These signals project via the optic nerve to the magnocellular layer of the lateral geniculate nucleus (LGN) then to layer 4Cα of the primary visual cortex (V1). The extrastriate areas that also receive these projections are the middle temporal visual area (MT or V5), the medial superior temporal visual area (MST) and the posterior parietal cortex (PPC).

Figure 1.11 *Cortical (in blue) and subcortical (in red) structures used in the brain for ocular movement control*

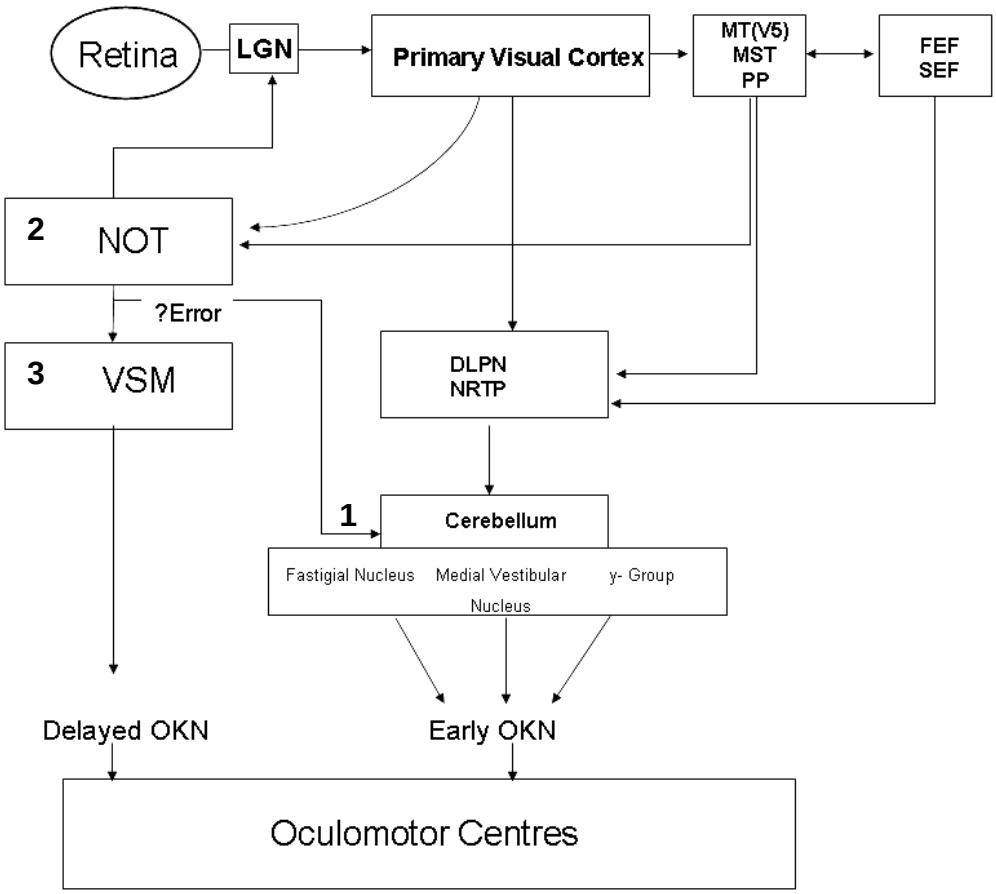


The signals are then passed to the frontal cortical areas of the frontal eye fields (FEF) and supplementary eye fields (SEF) which are involved in the generation of eye movements. Together the motor and sensory areas project to the pontine nuclei, in particular the dorso-lateral pontine nuclei (DLPN) and the nucleus reticularis tegmenti pontis (NRTP). The nucleus of the optic tract (NOT) located in the pretectum which receives input from MT and MST may also contribute to the neural pathways for OKN generation as it also has projections back to the LGN and to the pontine nuclei. Signals from the pontine nuclei then project to the cerebellum from which three nuclei, the fastigial, the medial vestibular, and y-group, project to the oculomotor neurons (Leigh & Zee, 2006, p25).

The *early* OKN response is mediated by the cortico-ponto-cerebellar pathway which is similar to the smooth pursuit pathway. The nucleus of the optic tract (NOT) may provide an error signal for the control of *early* OKN shown as *label 1* on Figure 1.12 (Fuchs, 1993; Garbutt & Harris, 1999).

The *delayed* OKN response is initiated by visual motion signals in the visual cortex. The nucleus of the optic tract is believed to be essential as an afferent signal to *delayed* OKN generation. This is shown as *label 2* on Figure 1.12. The delayed OKN response charges the *velocity storage mechanism* (VSM) in the brainstem highlighted with *label 3* on Figure 1.12 (Garbutt & Harris, 1999). Evidence from lesion studies affecting the NOT suggest this component of OKN is believed to be subcortical in origin (Fuchs, 1993).

Figure 1.12. *The basic neural pathways for horizontal OKN generation. NOT = nucleus of the optic tract, VSM= velocity storage mechanism, LGN = lateral geniculate nucleus, MT= middle temporal visual area (V5), MST = medial superior temporal visual area, PPC = posterior parietal cortex, FEF = frontal eye fields, SEF= supplementary eye fields, DLPN= dorsolateral pontine nuclei, NRTP = nucleus reticularis tegmenti pontis. Adapted from Leigh & Zee, 2006, p203 and Garbut & Harris (1999).*



1.4.3. Brain stem control of eye movements

The oculomotor nuclei involved with eye movements (III, IV and VI nuclei as shown in figure 1.11) are the origin of the three nerves innervating eye muscles, the oculomotor nerve (CNIII), the trochlear nerve (CNIV) and abducens nerve (CNVI).

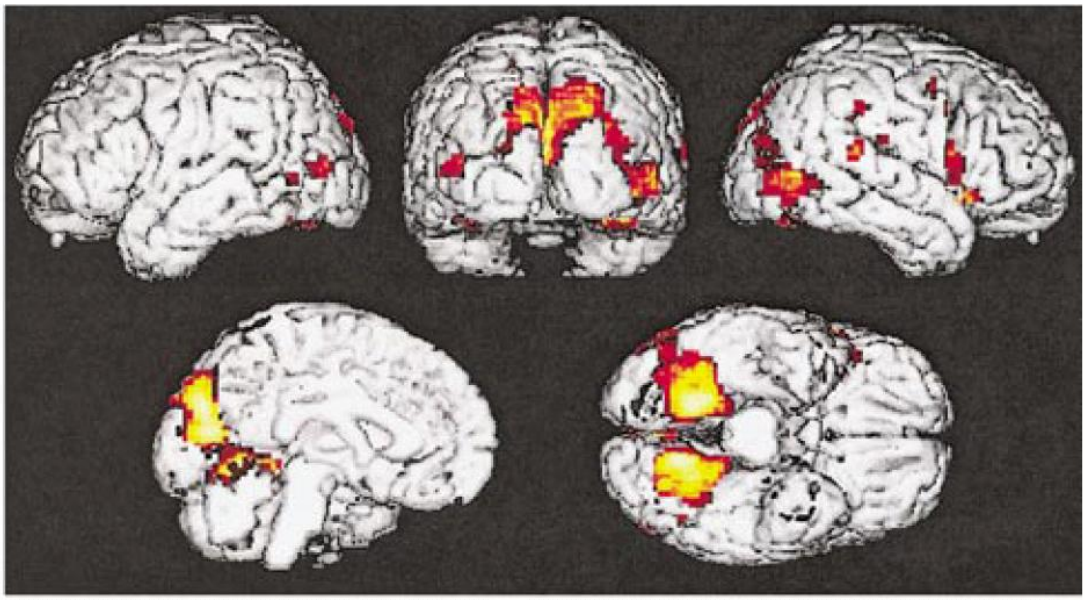
Projections from the abducens nucleus (innervating the ipsilateral lateral rectus muscle) through the medial longitudinal fasciculus to the contralateral oculomotor nucleus (CNIII) which innervates the contralateral medial rectus muscle permit binocular horizontal eye movement coordination. The vestibular nerve (CNVIII) projects to the medial vestibular nucleus sending excitatory projections to the contralateral CNVI nucleus and inhibitory projections to the ipsilateral CNVI nucleus. The CNIII nucleus also receives projections to initiate horizontal vergence movements (Ansons *et al.*, 2000).

The ocular motor neurons generating vertical and torsional eye movements lie in the CNIII and CNIV nuclei with vertical saccadic commands and gaze holding signals (from the neural integrator) being generated in the midbrain and vestibular and pursuit signals arising from the lower brain stem.

The above description of neurophysiological aspects of oculomotor control comes from both work done in animals and humans. More recently, functional magnetic resonance imaging (fMRI) performed in humans has been used to investigate areas of activation during OKN stimulation in humans. An area between the posterior thalamus and the mesencephalon has been shown to be activated in both horizontal and vertical OKN. For horizontal OKN increased activation also has been shown to occur bilaterally in the mediodorsal and dorsolateral ponto-medullary brainstem which is probably due to stimulation of the PPRF. During vertical OKN stimulation, additional activation has been found in the dorsal ponto-mesencephalic brainstem which is probably due to the ocular motor nuclei and the riMLF. Cerebellar activation has been shown to be the same for horizontal and vertical OKN and has been localized in both hemispheres, vermis, and parts of the flocculus, bilaterally (Bense *et al.*, 2006). Figure 1.13 shows activation of visual

motion areas during torsional optokinetic nystagmus. Responses from the calcarine to parieto-occipital and to ventral and lateral temporo-occipital cortex and the anterior insula are shown to be active during tOKN stimulation (Kleinschmidt *et al.*, 2002).

Figure 1.13 *Visual motion areas active during torsional optokinetic (tOKN) stimulation. The areas shown represent those that had greater activity during stimulus rotation compared to when the stimulus was stationary. (From Kleinschmidt et al (2002)).*



1.4.4. Neurophysiology of torsional eye control.

1.4.4.1 Rostral interstitial nucleus of the medial longitudinal fasciculus (riMLF)

Vertical and torsional saccades are generated in the rostral interstitial nucleus of the medial longitudinal fasiculus (riMLF). This structure lies adjacent to other mesencephalic

(midbrain) reticular nuclei, and especially near to the interstitial nucleus of Cajal (INC) which are shown in Figure 1.11 (Buttner-Ennever & Buttner, 1978; Büttner-Ennever & Buttner, 1988; Horn & Buttner-Ennever, 1998). The anatomic connections of the riMLF includes both excitatory and inhibitory burst neurons for vertical and torsional saccades and quick phases (Buttner *et al.*, 1977; Moschovakis *et al.*, 1991a; Moschovakis *et al.*, 1991b; Crossland *et al.*, 1994; Moschovakis *et al.*, 1996). Each riMLF contains neurons that burst for upward and downward eye movements but for torsional quick phases in only one direction. The right riMLF discharges for quick phases directed clockwise with respect to the subject, i.e. the top poles of both eyes are rotated towards the side that is activated (Moschovakis *et al.*, 1991a; Moschovakis *et al.*, 1991b).

Unilateral lesions of lesions of the riMLF cause contralesional torsional nystagmus (Suzuki *et al.*, 1995).

1.4.4.2. Interstitial nucleus of Cajal (INC).

The interstitial nucleus of Cajal (INC) is thought to be the neural integrator for torsional eye movements and involved in torsional and vertical gaze holding and the torsional and vertical vestibular-ocular reflex (VOR) (Fukushima *et al.*, 1992; Crawford & Vilis, 1993). It receives vertical and torsional saccadic inputs from the riMLF and vestibular inputs from the MLF. The neurons found within respond to velocity – position signals (Fukushima, 1987; Crawford *et al.*, 1991; Fukushima *et al.*, 1992; Fukushima & Kaneko, 1995).

Torsional movement in the clockwise direction has been found to correspond to activity in neurons of the right INC and counter clockwise torsional movement to activity in the left INC (Helmchen *et al.*, 1996).

1.4.4.2.1. Function of the interstitial nucleus of Cajal (INC).

Helmchen *et al.* (1998) investigated the function of the INC in the neural integration of different types of eye movement by using multiple muscimol micoinjections. In total, they used 13 unilateral and three bilateral INC inactivations by muscimol microinjections were used in four alert monkeys. Three-dimensional eye movement recordings were made during vertical and torsional vestibular ocular reflex.

During static testing with unilateral INC injections, a shift of Listing's plane to the contralesional side occurred. The monkeys showed a spontaneous torsional nystagmus with a downbeat component. A gaze holding deficit for torsional and vertical eye positions was found. Bilateral INC injections reduced the shift of Listings's plane caused by unilateral injections and additional up beating nystagmus was also noted.

During dynamic testing when unilateral INC injections were used, this had virtually no effect on torsional and vertical VOR gain and phase. During bilateral INC injections, torsional and vertical VOR showed gains reduced by 50%. The authors concluded that vertical and torsional nystagmus after INC lesions is caused by vestibular imbalance as well as neural integrator failure. This supports the theory that there are multiple neural integrators in the INC with parallel processing.

1.4.4.3. Middle temporal visual area (MT)

In primates, the conscious awareness of motion has been demonstrated to occur at the middle temporal (MT) area of the visual cortex. The role of MT has been investigated by looking at the effect of chemical lesions on visual perception thresholds (Newsome & Pare, 1988). Lesions were created in MT by injections of ibotenic acid, a neurotoxin. A direction discrimination task was used in which a threshold intensity at which the monkey could successfully discriminate motion was measured. In addition, a contrast task was used in which the monkeys were assessed on how well they could distinguish the orientation of stationary gratings. Results demonstrated no change in contrast thresholds following the lesion of the MT, however, significant elevation in motion thresholds was observed. This suggests that there is selectivity for motion perception in activation areas of MT.

In humans, the MT area has also been shown to be a site of strong activity during visual motion. Using position emission tomography to measure regional cerebral blood flow, Zeki *et al.*(1991) contrasted blood flow maps when subjects viewed moving and stationary black and white random square patterns. Results demonstrated a distinctive area within the temporo-parieto-occipital junction. This finding also corresponds with the way the visual cortex in the macaque monkey is organized with different areas of pre-striate cortex being responsible for different visual functions.

1.4.4.4. Medial superior temporal area (MST)

The medial superior temporal visual area (MST) connects to the inner border of the MT area. It receives projections from MT and sends projections to the inferior parietal lobule (Mesulam *et al.*, 1977). It has similar properties to the MT in that it contains

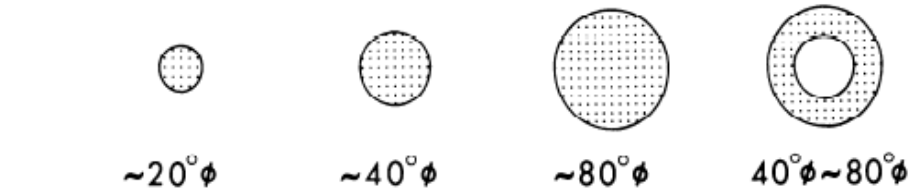
directionally sensitive cells; however the receptive fields of the cells within the MST area are larger. Saito *et al*.(1986) found cells in macaque monkeys that responded to torsional field motion, in both clockwise and anticlockwise directions. These cells were found in the dorsal part of the MST along with cells that respond to expansion / contraction and direction cells which respond to straight front-parallel motion in a particular direction.

1.4.4.4.1. Role of the cells within MST

The functional role of the cells within the MST has been examined (Tanaka & Saito, 1989). It was found that rotation cells that responded to clockwise and anticlockwise stimulation were equally as common. Of the 50 cells sampled, 25 responded to clockwise motion and 25 to anticlockwise motion. This was in contrast to expansion / contraction cells where those that responded to expansion were more common. Figure 1.14 shows the effect of changing the areal extent of the stimulus on the response of rotation cells within the MST. In general, all types of cells were found to respond optimally when the field of motion exceeded 40° in diameter. It was also found that an annular stimulus, with the central portion missing, also elicited a good response.

Figure 1.15 illustrates the response of rotation cells at various speeds of rotation. It was found that rotation cells classified as *"R1"* cells responded at a limited range of speeds used, depicted on the top panel of Figure 1.15. In addition, Figure 1.15 shows a group of rotation cells that were found to respond to a whole range of speeds, referred to as *"R2"* cells. Tanaka & Saito (1989) suggested the possible types of movement that the properties of these cells reflect are motion caused by movement of the animal itself, as this would cause wide field motion of the surround.

Figure 1.14 *Changing of the areal extent of the stimulus in relation to the response of rotation cells with the stimulus moving in clockwise and anticlockwise directions (from Tanaka & Saito, 1989)*



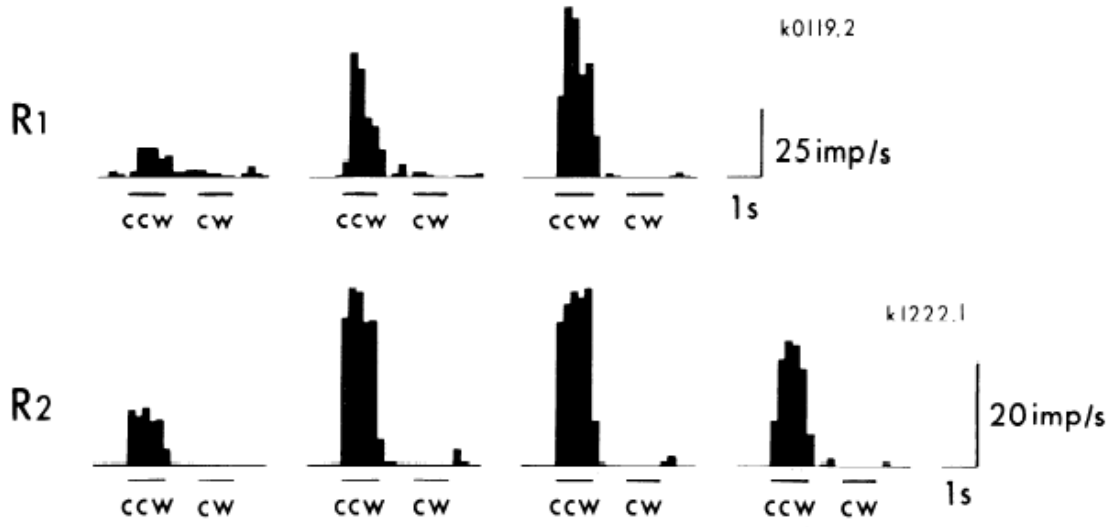
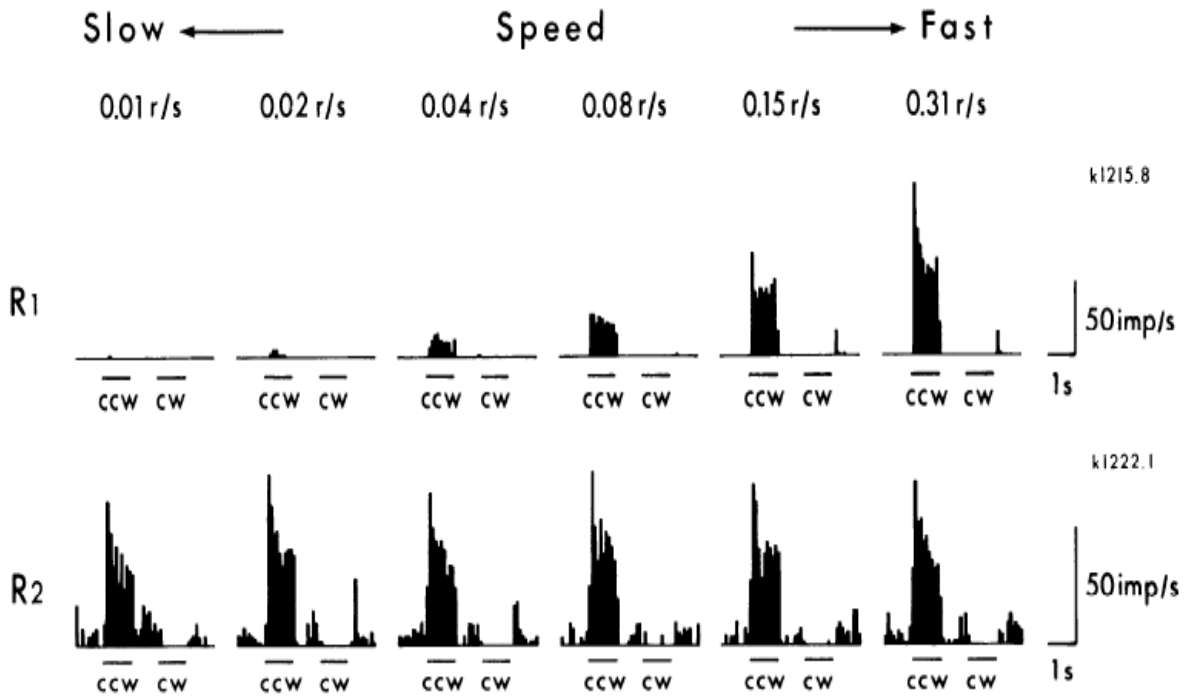


Figure 1.15 *Response of rotation cells to rotation at various speeds showing cells that responded over a limited range of stimulus velocities (R1) and those that responded well over a large range of velocities (R2) (from Tanaka & Saito, 1989).*



1.4.4.5. Binocular optic flow

The motion of one's self, as occurs during walking or travelling in a car, produces a visual flow field on the retina known as optic flow (Gibson, 1954). The specific flow fields generated are influenced by the direction of travel and direction of gaze (Angelaki & Hess, 2005). The flow fields generated are thought to aid in visual spatial orientation and visual navigation. These result in reflexive short latency eye movements so that foveal acuity and stereovision is maintained. The dorsal MST area contains cells that respond to wide field motion rotational motion of the visual environment at varying speeds (discussed in section 1.4.4.4.). Rotational optic flow fields of the visual environment are likely to be stimulated when an animal moves its eyes, head and/or body while moving forward in space (Tanaka & Saito, 1989).

1.5. Areas of investigation

A discussion of the key areas of investigation in this thesis follows, namely, the response characteristics of torsional optokinetic nystagmus in (i) normal subjects (sections 1.5.1.,1.5.2. and 1.5.3) and (ii) patients with ocular motor disorders (sections 1.5.4. and 1.5.5.).

1.5.1. Normal response characteristics

1.5.1.1. The effect of stimulus velocity on OKN generation

There are only a few reports in which the gain (eye velocity in relation to stimulus velocity) of tOKN to various stimuli has been systematically investigated. It has been described to be considerably less than hOKN and vOKN response with some reported gain values of below 0.1 (Collewijn *et al.*, 1985; Cheung & Howard, 1991; Seidman *et al.*, 1992; Morrow & Sharpe, 1993; Suzuki *et al.*, 2000). For hOKN, the gain can be as much as 0.8 for stimuli less than 60º/s (Baloh *et al.*, 1982; van den Berg & Collewijn, 1988; Fletcher *et al.*, 1990) although the SPV for hOKN has been shown to decline above 80 – 90°/s stimulation (Holm-Jensen & Peitersen, 1979). For vOKN, the gain is lower than hOKN, with reported values of approximately 0.7 or greater for slow stimulus velocities up to 12°/s decreasing to approximately 0.3 and 0.4 to downwards and upward stimulation, respectively, at 70°/s stimulation (Murasugi & Howard, 1989b; Garbutt *et al.*, 2003b). The consistency of the vOKN response has also been reported as poor above 60°/s (Wei *et al.*, 1992).

In all the previous reports into tOKN, there was a small range of stimulus velocities used, the largest range being from 10-80°/s in only 5 subjects (Morrow & Sharpe, 1993). Reported gain values were also variable across subjects.

1.5.1.2. The effect of central and peripheral stimulation

1.5.1.2.1. Torsional OKN

The effect of central and peripheral stimulation on the tOKN response has been investigated in only one previous study using four subjects (Howard *et al.*, 1994). The authors use a series of artificial central and peripheral masks to occlude various proportions of the stimulus. Their results demonstrated that the tOKN response was dominated by central stimulation as the gain increased with increase of central field size.

1.5.1.2.2. Horizontal OKN

Abadi *et al.* (2005) investigated the *rise time* of the maximum slow phase hOKN velocity (time taken to reach 63% or 90%, i.e. the early OKN response). They found this to be no different when viewing a central field stimulus of 20° diameter or when the central field is occluded by a 12° diameter mask. They concluded that this indicated that both central and peripheral stimulation share common mechanisms to elicit the early component of hOKN. The gain in this study was lower when the central field was occluded with the 12° mask compared to full field and central field stimulation

The absence of central vision in patients with central scotomas due, for example, to age-related macular degeneration has also been shown not to significantly affect the hOKN response (Abadi & Pantazidou, 1997; Valmaggia *et al.*, 2001). It has also been

demonstrated that a *'filling–in'* response occurs when OKN is elicited in these patients (Valmaggia & Gottlob, 2002).

1.5.1.2.3. Vertical OKN

When testing vOKN and the contribution of the central and peripheral retina, the up/down asymmetry (i.e. stronger upwards) has been shown to increase after the central field was occluded at stimulus velocities above 30°/s in 6/10 subjects. In 3/10 subjects reduced gains were observed in both directions resulting in a symmetric up/down response. When viewing a central 6° wide strip, no difference in vOKN was noted compared to full field stimulation (Murasugi & Howard, 1989b).

1.5.1.3. The effect of aging on OKN generation

The change in the hOKN response with age has been extensively researched and has been shown to undergo a mild but significant deterioration during senescence (Spooner *et al.*, 1980; Simons & Buttner, 1985; Kato *et al.*, 1994; Valmaggia *et al.*, 2004). This has been attributed to age-related degeneration in cortical areas responsible for motion perception and in the retino-geniculate pathway but degeneration of ocular motor areas cannot be discounted (Tran *et al.*, 1998).

The effect of aging on vOKN has also been investigated and similarly the OKN response in younger subjects has been found to be superior to that found in elderly subjects (Demer, 1994).

Since the early component of horizontal and vertical OKN is closely linked to the pursuit system, it has been postulated that changes in the pursuit system with aging would

also influence the OKN system (Simons & Buttner, 1985). The literature in this area shows a general agreement that the pursuit system also deteriorates with age (Spooner *et al.*, 1980; Simons & Buttner, 1985; Demer, 1994; Bono *et al.*, 1996; Knox *et al.*, 2005). Torsional OKN however, is not linked to the pursuit mechanism as little or no movement occurs at the fovea when a subject fixates the stimulus (Thilo *et al.*, 1999). There is no previous work on the tOKN response and normal aging. It would be of interest, therefore, to see how age influences the tOKN system in comparison to previously published results on hOKN and vOKN given that it operates from a reflexive OKN system with probably no pursuit input.

1.5.2. Abnormalities of the OKN system

Abnormalities in optokinetic nystagmus can occur in all three directions of eye rotation. They may manifest in:

- A complete absence or selective absence of either phase of the response.
- Asymmetry in direction of response (egg. strabismus).
- A change in a pre-existing ocular motor disorder (e.g. infantile nystagmus).

Clinically, this could result in a patient using compensatory behaviors to overcome the disturbance in the OKN system. An abnormality may also reflect abnormal visual development or be an indicator to acquired pathology of the visual pathway, vestibular system or cerebellum.

1.5.2.1. Absent or selective absent OKN

A complete lack of a hOKN response can sometimes signify very poor visual acuity as an OKN stimulus is very difficult to ignore voluntarily. However quantifying the level of visual acuity using OKN stimuli is not a clinically reliable method as many factors need to be controlled to elicit a reliable response (Garbutt & Harris, 1999).

Saccadic initiation failure (SIF or ocular motor apraxia) affects the fast phase of the OKN response and can occur in horizontal or vertical directions (Zee *et al.*, 1983). This disorder can be idiopathic in origin and usually patients tend to adapt by using head movements to stimulate eye movements. Neurometabolic diseases such as Nieman pick type C and Gaucher Disease can also be associated with SIF (Neville *et al.*, 1973; Vivian *et al.*, 1993) . A unilateral or bilateral lesion of the hOKN pathway in the cortex, brainstem or cerebellum will result in defective OKN towards the side of the lesion or an absence of any response, respectively. Vertical OKN, can be defective following a lesion of the rostral midbrain (Garbutt & Harris, 1999). The tOKN response has been shown to be affected after unilateral vestibular loss (Lopez *et al.*, 2005). An increase of the tOKN slow phase was present when the tOKN stimulus was rotated towards the same side as the lesion and was decreased when the stimulus was rotated to the contralesional side.

1.5.2.2. Asymmetry in direction of response: OKN in strabismus

Strabismus with early onset from birth onwards can result in unequal visual inputs to both eyes and this causes an interruption of normal visual development (Schor & Levi, 1980; Hine, 1985; Schor *et al.*, 1997; Westall *et al.*, 1998). Strabismus, manifest from birth, is most commonly in the esotropia direction (Schor *et al.*, 1997). This can be

accompanied by dissociated vertical deviation (DVD) and latent nystagmus (LN) referred to as essential infantile esotropia syndrome (EIES) (previously referred to as congenital squint syndrome) (Von Noorden, 1990a). DVD clinically presents as an elevation and extorsion of either eye under cover (Van Rijn *et al.*, 1997; Guyton, 2000; Brodsky & Tusa, 2004). It has been postulated that it is a mechanism to dampen torsional and vertical latent nystagmus present (Irving *et al.*, 1998). The latent nystagmus similar to DVD appears as each eye is covered. A horizontal jerk nystagmus is usually present in which the quick phase of each eye beats towards the uncovered (fixating) eye (Leigh & Zee, 2006, p 73).

1.5.4.2.1. Horizontal OKN and strabismus

The development of a symmetrical monocular hOKN response is influenced by abnormal visual experience in early life. The poorly developed optokinetic response for the temporalward direction normally found at birth can persist when a disruption of visual development due to strabismus occurs. This usually affects both eyes if the strabismus occurred at very early onset or can just be present monocularly (Schor & Levi, 1980; Westall & Shute, 1992).

Although the temporalward response has been primarily highlighted to be defective in previous literature, the nasalward response has been shown to be abnormal in severely amblyopic patients at high stimulus velocities (Schor & Levi, 1980; Mohn *et al.*, 1986; van Hof-van Duin & Mohn, 1986). The persistence of the hOKN asymmetry has been linked to the lack of binocular visual development (Valmaggia *et al.*, 2003) as both are said to follow a similar time course. However this has been contradicted by findings of symmetrical OKN responses in patients with no stereopsis (Demer & Von Noorden, 1988).

Furthermore, patients with strabismus from birth who were surgically realigned and developed a high level of binocular vision still demonstrated an asymmetrical hOKN response (Aiello *et al.*, 1994; Wright, 1996b).

Further exceptions to the link between binocular vision and symmetrical hOKN development come from studies in which patients have profound monocular visual loss. Shawkat *et al.* (1995) describe the OKN responses of patients with uniocular visual deprivation who were born with microphthalmus and persistent hyperplastic primary vitreous compared with ten aphakic children treated for congenital unilateral cataracts. All patients with unilateral cataracts showed statistically significant monocular naso-to-temporal asymmetry for either eye. Subjects in the group with profound monocular deprivation had symmetric OKN. Day (1995) examined visual development in thirty-six *monocular* subjects (one clinically normal eye, and one absent (enucleated) or with profound visual loss) and compared the results to a group of subjects with infantile esotropia and normal subjects. It was found that visual development measures in monocular individuals' bore greater resemblance to the normal subjects than those with infantile esotropia. Thus the author concluded that the development of motion processing is affected by abnormal experience in the first year of life. A distinction was made by the authors between *monocular* patients, as having no binocular competition between the eyes during development and patients that do, such as those with infantile esotropia.

1.5.4.2.2. Vertical OKN and strabismus

The vOKN response has been shown to be prone to similar developmental disruptions, however there is disagreement in the literature regarding the direction of

stimulation that is affected the most. Binocular vOKN stimulation for stimuli moving downward has been shown to be *reduced* in patients with early onset strabismus compared to patients who developed strabismus later (Tychsen *et al.*, 1984). This indicates persistence of the up/down asymmetry found at birth (Matsuo & Cohen, 1984; van den Berg & Collewijn, 1988; Murasugi & Howard, 1989b; Bohmer & Baloh, 1990; Ogino *et al.*, 1996; Garbutt *et al.*, 2003a; Garbutt *et al.*, 2003b). In adults that had a disruption of visual development including childhood strabismus leading to amblyopia, a reduction of slow phase velocity to upward OKN stimulation has been reported (Schor & Levi, 1980). Garbutt *et al.* (2003b) also reported in six patients with strabismus since childhood, a reduced vOKN to downward moving stimuli although some of the patients showed the opposite response. They also reported an inappropriate diagonal response to stimulation of the vertical optokinetic stimulus that did not occur in normals. Garbutt *et al.* (2003b) were unable to conclude whether factors such as DVD, level of amblyopia or age of onset were contributors to the abnormal responses as only six patients were used in the study.

1.5.4.2.3. Torsional OKN and strabismus

There is no previous research on the effect of early interruption of binocular vision development due to infantile esotropia syndrome or strabismus during childhood on tOKN. Washio *et al.* (2005) looked at the effect of horizontal image disparity using prisms and alteration of the viewing distance. Although this was done in normal subjects, the creation of an image disparity could serve as a model for what could happen in strabismus where ocular misalignment results in image disparity between the two eyes. They found a significant reduction tOKN gain to all conditions where a horizontal disparity was

induced. Washio *et al.* (2005) concluded that as tOKN functions from a purely reflexive OKN system, this was evidence to suggest that the tOKN system was also affected by horizontal disparity. This observation is also indicative of the possibility that tOKN could be affected in subjects who have had ocular misalignment since birth or childhood. Furthermore as previously discussed, there appears to be a definite effect on both hOKN and vOKN systems when early visual development is disrupted. It would therefore be of interest to see any disruption is evident in tOKN with the presence of strabismus.

1.5.4.3. Optokinetic nystagmus in infantile nystagmus.

Infantile nystagmus (IN) is an involuntary ocular oscillation that occurs secondary to other ocular pathology such as sensory visual deprivation and other ocular development disorders, or can be idiopathic in nature. In 25% of cases it is associated with albinism and in 10% of cases it is identified with visual or ocular defects (Abadi & Bjerre, 2002). It is present either at birth or develops during infancy and for this reason it is also be referred to as infantile nystagmus syndrome (Gottlob, 1997; Hertle & Dell'Osso, 1999; Hertle *et al.*, 2002). Clinically, IN usually presents in the horizontal direction without changing direction in up or down-gaze and is conjugate. Typical eye movement waveforms described by Dell'osso & Daroff (1975) found in IN are displayed in Figure 1.16.

A torsional component to the infantile nystagmus has also been reported although it has been described as difficult to detect as it is often phase locked with the horizontal nystagmus (Abadi & Dickinson, 1986; Averbuch-Heller *et al.*, 2002). In a group of 13 patients with IN, the torsional nystagmus component ranged from 8.2% to 94.4% (median 32.9%) of the peak to peak magnitudes (Averbuch-Heller *et al.*, 2002).

1.5.4.3.1. OKN characteristics in the presence of IN.

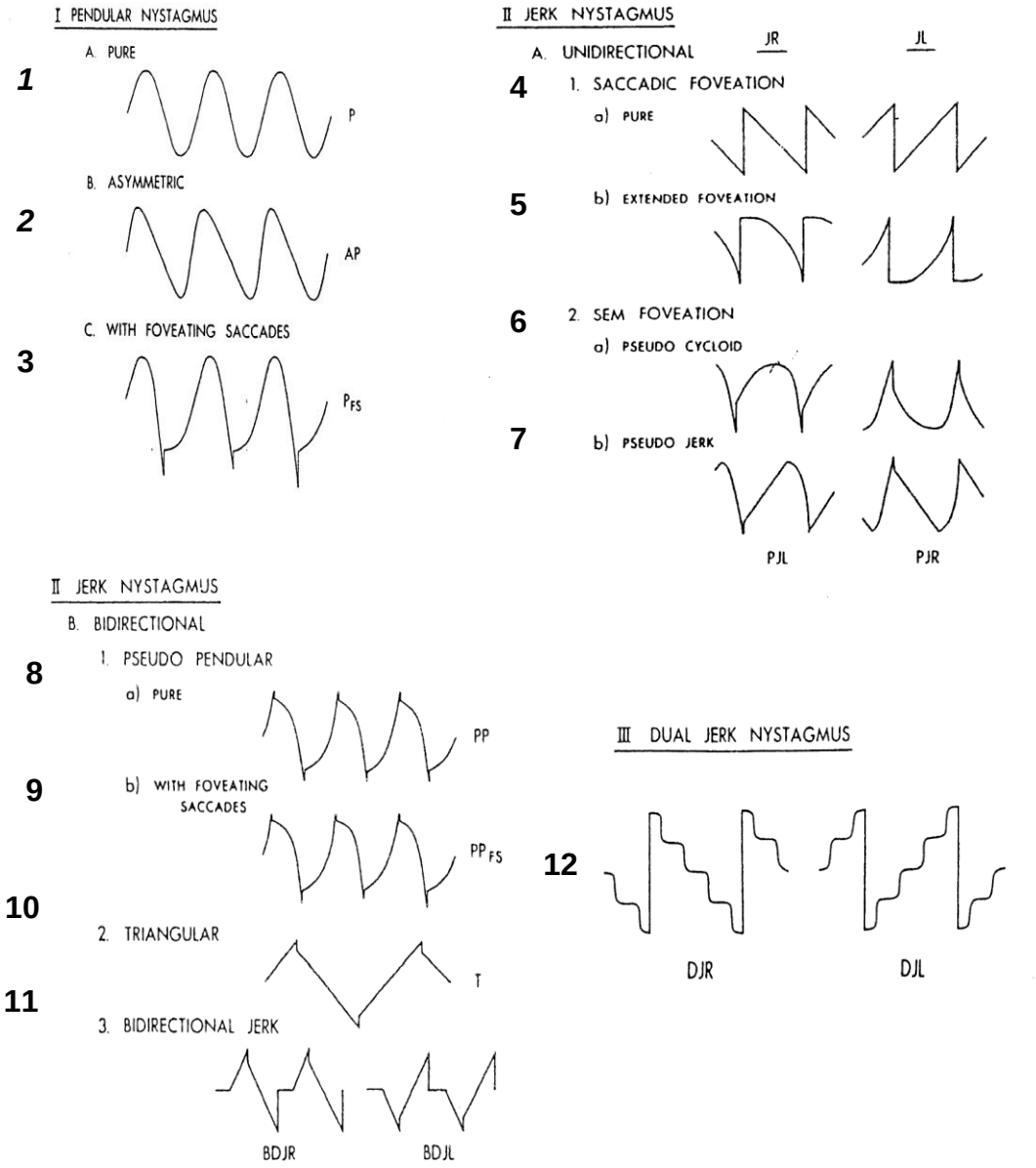
The response to OKN stimuli in IN subjects is controversial in the literature. When IN patients view horizontal optokinetic stimuli an inversion of the response has been described such that the quick phase of the OKN response is directed towards the same side as the direction of the stimulus (Halmagyi *et al.*, 1980). Normally, as described previously, the *slow* phase of the OKN response moves with the direction of the stimulus with the quick phase moving in the opposite direction. A complete absence of OKN response in IN subjects has been described, with no change demonstrated in pre-existing oscillations when viewing the OKN stimulus (Harris, 1997). In addition, a change in the point where the nystagmus is the smallest in magnitude, called the null point, may also occur in IN patients when viewing optokinetic stimuli. Suppression of IN has also been documented (Harris, 1997).

If the infantile nystagmus is in the vertical direction, responses to horizontal optokinetic stimuli have been reported as normal. When the vOKN response is tested in patients with horizontal infantile nystagmus, a variation of symmetrical and asymmetrical responses have been described (Halmagyi *et al.*, 1980; Abadi & Dickinson, 1985).

Additionally, a gaze modulated response has been observed in patients with horizontal infantile nystagmus when subjects viewed the hOKN stimulus. This resulted in them showing an absent typical saw tooth OKN response but instead when the stimulus moved to the right the subject displayed the nystagmus that was usually present in right gaze and vice versa for OKN stimulus movement to the left. The authors concluded that the presence of infantile nystagmus caused an adaptation of the OKN response (Abadi & Dickinson, 1985).

The effect of infantile nystagmus on torsional OKN generation has not been previously described and therefore it would be of interest to see how the response is affected in this dimension, particularly if a torsional component to the nystagmus is present in addition.

Figure 1.16. *The 12 infantile nystagmus waveforms described by Dell'Osso & Daroff (1975). Categories of nystagmus are pendular (1-3), unidirectional jerk (4-7), bidirectional jerk (8-11) and dual jerk nystagmus (12).*



1.6. Summary

The optokinetic (OKN) system working alone or in combination with the vestibular and smooth pursuit systems provides compensatory eye movements to stabilize image motion of the visual field. Certain aspects of the horizontal OKN response have been linked to the smooth pursuit system. The early OKN response probably shares similar properties to smooth pursuit (Fuchs, 1993). The symmetrical development of the response is thought to coincide with the normal development of the smooth pursuit pathways (Jacobs *et al.,* 1997). Previous literature has shown horizontal and vertical OKN have a higher gain (eye velocity in relation to stimulus velocity) to reported values of the torsional OKN response (Baloh *et al.*, 1982; van den Berg & Collewijn, 1988; Murasugi & Howard, 1989b; Fletcher *et al.*, 1990; Garbutt *et al.*, 2003b). The horizontal OKN system appears to show no difference in response when a central field stimulus is used compared to a full field stimulus (Abadi *et al.*, 2005). A small reduction in hOKN and vOKN responses with aging has been noted for which one explanation has been related to smooth pursuit deterioration with age (Spooner *et al.*, 1980; Simons & Buttner, 1985; Demer, 1994; Bono *et al.*, 1996; Knox *et al.*, 2005).

The normal response characteristics of the torsional OKN (tOKN) response have not been researched in any great depth. We know that there is probably little or no input from the smooth pursuit system to the response (Thilo *et al.*, 1999), therefore it would be of interest to note how tOKN behaves in response to a wide range of stimulus velocities. It would also be of interest to vary areas of stimulation to allow comparison to horizontal and vertical OKN systems. There is no previous research on the effect of aging on the

response, and any further insight into this would give us further information about how this purely reflexive OKN system is affected by normal aging.

Specific defects in the horizontal and vertical OKN systems have been described with the presence of strabismus from birth, namely asymmetric OKN responses. With horizontal OKN, the temporalward response has been mainly found to be reduced (Schor & Levi, 1980; Westall & Shute, 1992). There is less consistency in reports relating to vertical OKN response with some reports stating a reduction in downward OKN motion (Tychsen *et al.*, 1984) and some for upward motion (Schor & Levi, 1980) or both (Garbutt *et al.*, 2003b).

The presence of infantile nystagmus has also been shown to affect OKN responses. Descriptions of horizontal OKN stimulation responses range from an absence of OKN (Garbutt & Harris, 1999) to an adaptation of the response (Halmagyi *et al.*, 1980; Abadi & Dickinson, 1985). Changes to the pre-existing infantile nystagmus have also been reported (Harris, 1997). There is no previous research on the effects of strabismus and infantile nystagmus on the torsional optokinetic system and so further study into this area would give us information to see whether the tOKN response displays similar developmental abnormalities to the other OKN systems.

1.7. Aims

The aims of this thesis were to:

1) Systematically investigate the relationship between stimulus velocity and the gain of torsional optokinetic nystagmus by using a large range of stimulus velocities to establish the limit and optimum level of response.

2) Examine the effects of central and peripheral stimulation on the torsional optokinetic response by varying the size of central and peripheral field.

2a) Determine the influence of filling-in on torsional optokinetic nystagmus, since previous reports have described a filling-in response when central portions of the stimulus were occluded in horizontal optokinetic nystagmus.

3) Examine the effects of normal aging on the torsional optokinetic response.

4) Investigate the torsional optokinetic response in adults with longstanding strabismus due to essential infantile esotropia syndrome (EIES) and childhood strabismus (CS).

5) Investigate the torsional optokinetic nystagmus response in adults with infantile nystagmus (IN).

2. Materials and methods

2. Materials and methods

2.1. Subjects

2.1.1. Normal volunteers

The eye movements of 20 healthy subjects aged from 20 to 59 years were examined (15 female and 5 male, mean age 34.9 years, SD 12.2 years) for experiment 1, "The *effect of stimulus velocity on tOKN generation*" and experiment 2, "*The effect of central and peripheral stimulation on tOKN generation".*

A further 30 healthy subjects were included in experiment 3, *"The effect of aging on tOKN generation,"* aged between 19 and 72 years (19 female and 11 male, mean age 50.1 years, SD 18.1 years). A proportion of normal subjects from experiment 3 also served as age-matched control subjects for the patient groups in experiments 4, *"tOKN in strabismus"* and experiment 5, *"tOKN in infantile nystagmus"*.

All subjects had normal corrected visual acuity of (6/6 or better in each eye for experiments 1 and 2 and 6/9 or better in the viewing eye for experiment 3). An orthoptic examination was performed to exclude any ocular motility and binocular vision defects. All tests were performed without refractive correction or with contact lenses where refractive correction was necessary. Six subjects from experiment used in experiments 1 and 2 had mild myopia or myopic astigmatism but were able to see the stimuli clearly from a distance of 120cm without refractive correction.

All volunteers reported that they were free from any neurological or otological problems. Nine of the 30 subjects in experiment 3 were on medication for either hypertension (n=4), lowering cholesterol (n=4), diabetes (type II diabetes mellitus, n=2) or

hiatus hernia (n=1). Seven of the volunteers on medication were in the over 65 year old age group.

All above normal volunteers were either recruited from the Ophthalmology Group at the University of Leicester or the Leicester Royal Infirmary, were colleagues of the researcher or were friends or acquaintances of the researcher and her colleagues.

All experiments for this thesis received local ethical approval and were performed with consent (written and oral) after explanation of the nature and possible consequences of the study via a subject information sheet. All experiments were performed in accordance with tenets of the Declaration of Helsinki.

2.2. Instrumentation

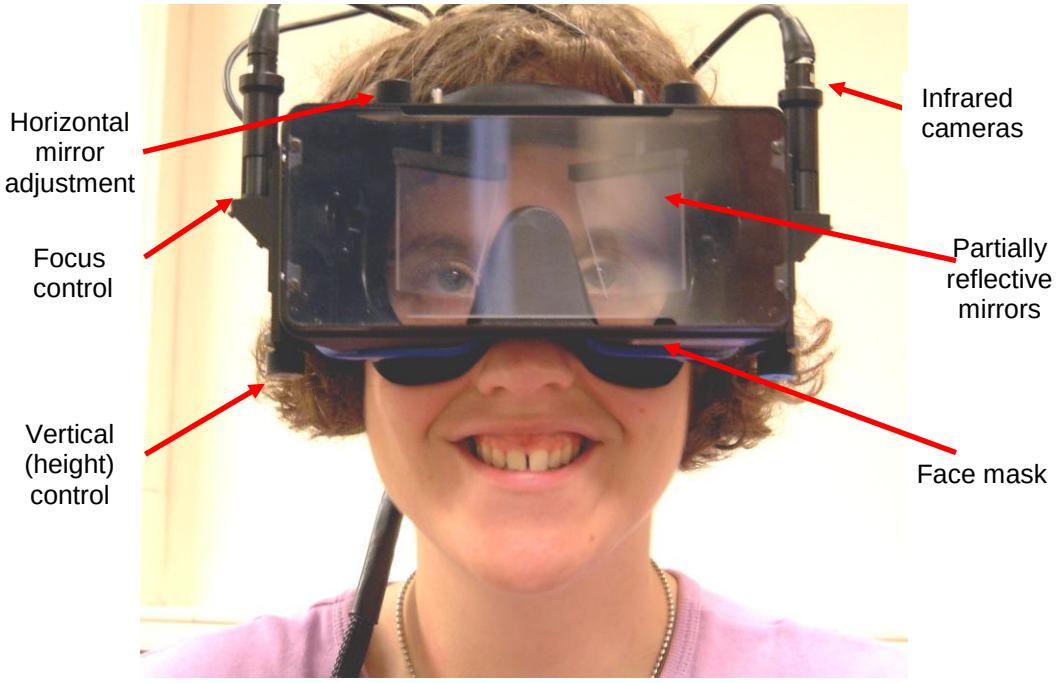
2.2.1. Eye movement recording

A video-oculography (VOG) technique was used to measure eye movements in three dimensions at a sampling rate of 50 Hz ("Strabs 3D VOG" system, Sensomotoric GmbH, Teltow, Germany). Figure 2.1 shows the VOG mask used to test torsional eye movements. This consisted of infra red video cameras fitted on to a face mask attached to the head using a rubber strap.

The system hardware consists of a PC workstation, signal processing units for both eye cameras and a power supply unit for infrared LEDs illuminating the eyes under the face mask. Pupil tracking was used to derive horizontal and vertical movements. A segment of the iris was tracked to measure torsional eye movements (described below). The system had a spatial resolution of 0.03º, 0.02º, and 0.1º and a linearity of ± 3.8%, ± 3.2% and ± 1.4% full scale reading for horizontal, vertical and torsional eye movements,

respectively (company specifications). The range of linear measurement was ± 25º, ± 20º and ±18º for horizontal, vertical and torsional eye movements, respectively. The noise for the setup was estimated from the torsional recordings as 0.1-0.2º root mean square for torsional angle and 0.1-0.15º/s root mean squared for torsional velocity.

Figure 2.1. *A subject wearing the "Strabs" 3D VOG goggles.*

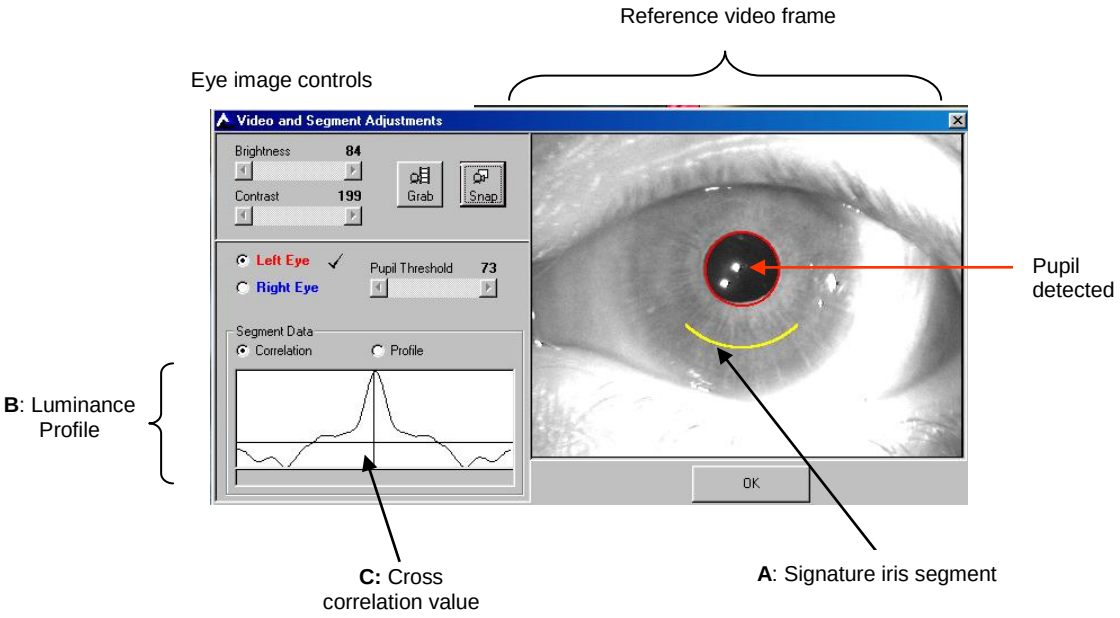


2.2.1.1. Measurement of torsional eye position

Figure 2.2 illustrates how the torsional eye position was ascertained during the VOG set-up. A section of the iris, the 'signature segment' (A, identified in yellow on Figure 2.2), was selected from a reference video frame. This included significant landmarks in the iris from which a luminance profile was measured (B). Torsional eye position was calculated from angular displacement of the defined segment. To estimate the torsional eye position, the luminance levels from subsequent video frames were cross-

correlated for the corresponding segment with the original signature segment. The cross-correlation value (C) also provided a measure of correspondence between the signature segment and a subsequent image which was used as an estimate of the quality of the recording. Data that exceeded a torsional quality of 0.5 were used for analysis (a correlation close to 1 implies the best data quality).

Figure 2.2. *Measurement of torsional eye position*



Poor quality data can result from any of the following reasons; iris segment without many landmarks; changing pupil size due to altered illumination leading to changes in the position of landmarks, and when the pupil is not accurately detected due to small size or interference from surrounding ocular structures (e.g. dark eye lashes or lashes with heavy eye makeup, droopy eye lids). If in the event that it was considered, from online recordings, that there was a possibility that the eye lids were occluding the recording, volunteers were instructed to “open their eyes wide”.

2.2.1.2. Experimental set-up

Figure 2.3 depicts the experimental set-up for recording torsional optokinetic nystagmus. All subjects sat upright with their head stabilized on a chin rest placed 120 cm away from a projection screen. The experimental stimulus was rear projected on to the screen of 1.75m width and 1.17 meters height using an LCD projector (model Epson EMP 703, resolution 1024x768 pixels). The stimuli were generated using a visual stimulus projector (VSG 2/5, Cambridge Research Systems, Rochester UK).

All experiments used a radial grating pattern to elicit torsional optokinetic nystagmus (tOKN) (examples of the tOKN stimulus are shown in ***Movie C***, ***Clip1 and 2*** in *additional addenda CD*). Figure 2.4 shows examples of the grating patterns in all experiments. The luminance of the grating pattern varied from 0.45 to 23.0 candelas/ m^2 giving a luminance contrast of 96%. The stimulus revolved around its central axis in both clockwise and anticlockwise directions to generate tOKN with variations in its velocity, cycle size of grating pattern and area of stimulation for different experimental conditions. While viewing the stimulus, subjects were always asked to stare at the whole stimulus keeping it as clear as possible and to avoid following any one particular area of the pattern.

The height of each subject was adjusted so that the centre of the stimulus projected on to the screen and the subject's eyes were at the same level. The cameras of the VOG system were adjusted while the subject viewed the stationary stimulus so that pupil size, threshold and contrast levels could be set at experimental conditions to ensure the highest quality of recording.

Figure 2.3. *The experimental set-up for recording torsional optokinetic nystagmus. The volunteer sits 1.2m from the rear projected tOKN stimulus, while wearing the 'strabs'*

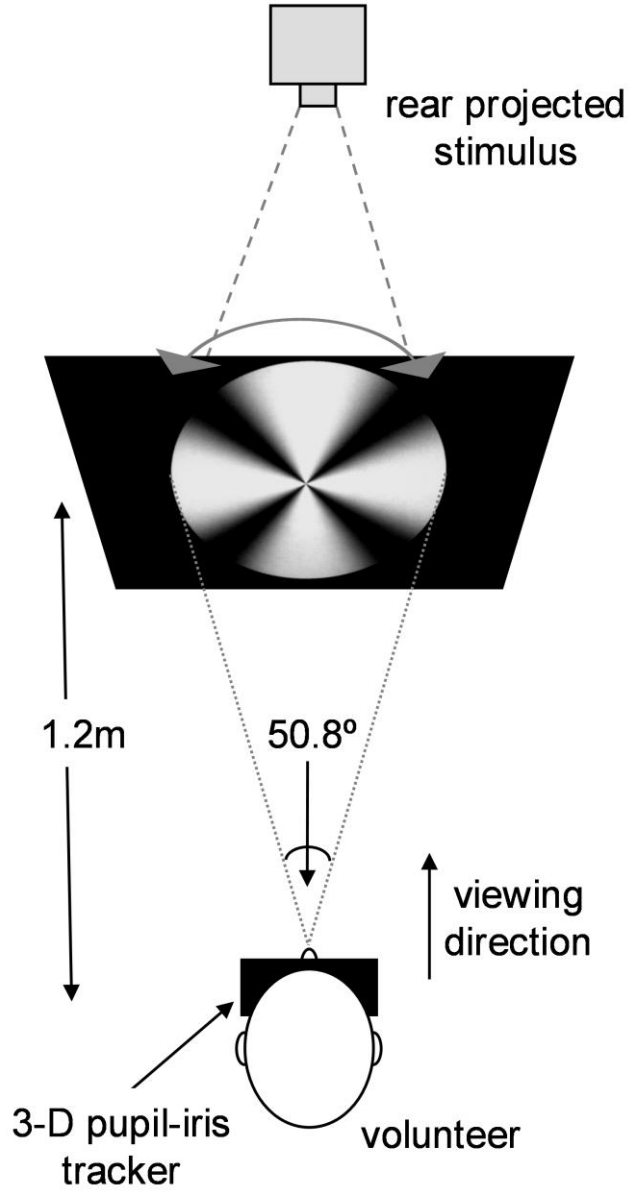
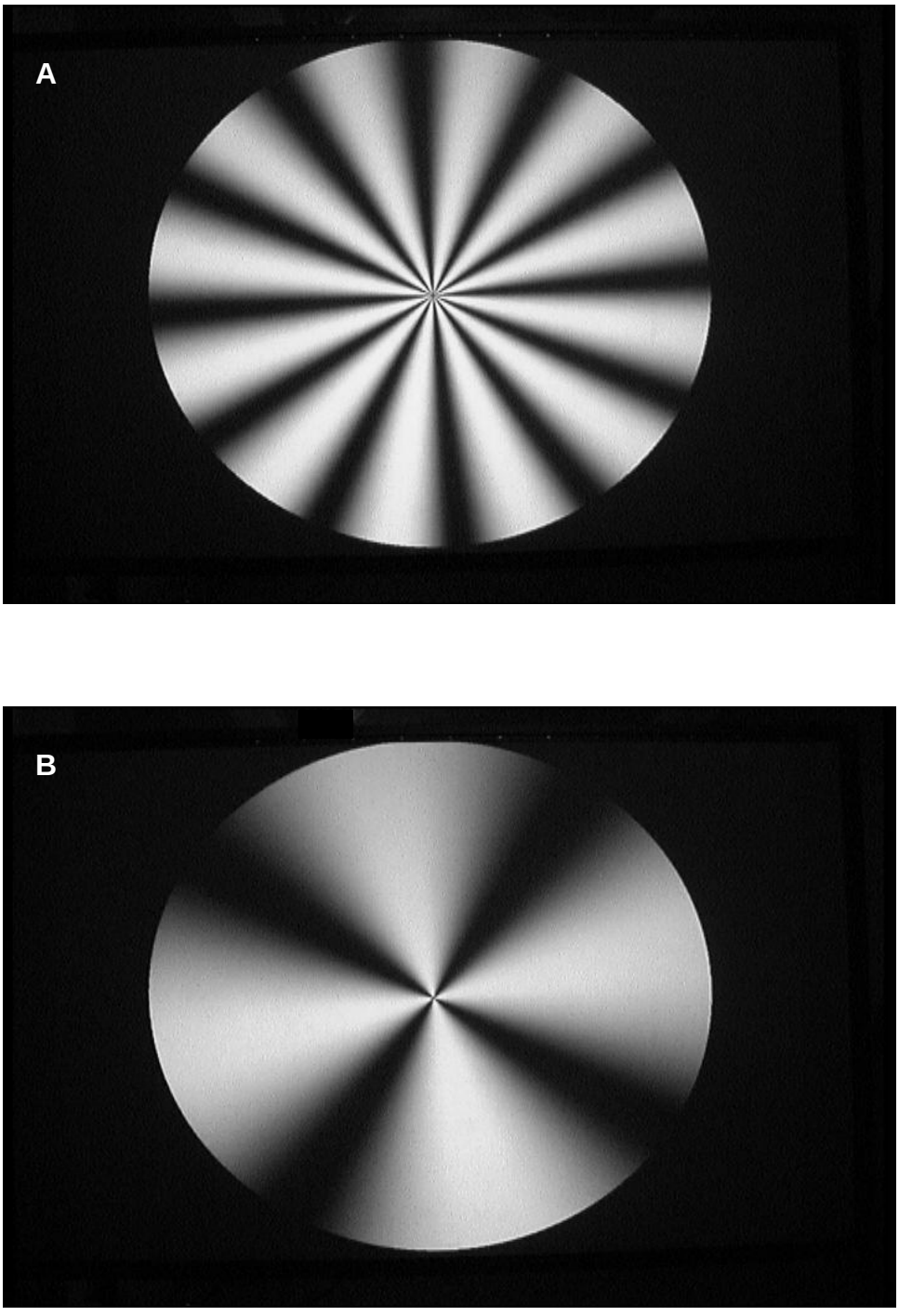


Figure 2.4. *Examples of grating patterns used in all experiments. Pattern (A) displays a stimulus of cycle size 30° and pattern (B) is of cycle size 90°. The stimulus could be revolved around its central axis in both clockwise and anticlockwise directions to generate tOKN.*

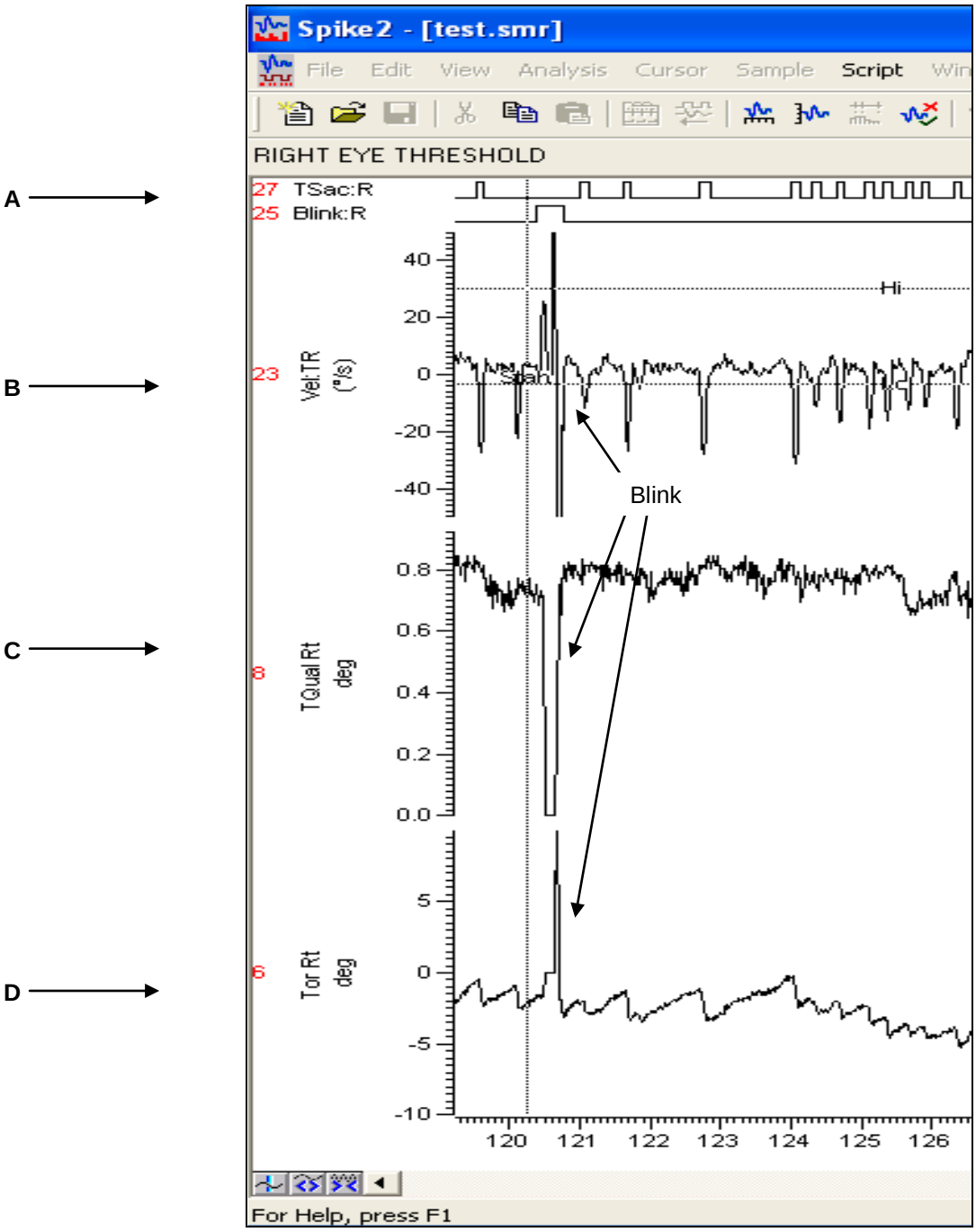


A five-point calibration of each eye was performed with the volunteers fixating points centrally, and 15º in depression, right gaze, elevation and left gaze. Torsional measurements were calibrated within the video–oculography set-up determined from rotations of the iris. The torsional angle was defined in relation to the initial image measured when setting up the experiment.

2.2.1.3. Torsional data analysis

The digitised ASCII file output for horizontal vertical and torsional data was converted into Spike 2 software files (Cambridge Electronic Design, UK) for analysis. Figure 2.5 shows an on-screen example of a Spike 2 file used during analysis. Smoothed velocity traces of the torsional data were created using a simple five-point low pass differentiator filter (boxcar). A velocity threshold of 10º/s, shown as channel B on Figure 2.5 was used as a default to determine saccades (labeled as channel A in the torsional recording (D)). Since the level of noise varied depending on the quality of the torsional recording (label C on Figure 2.5), the velocity threshold could be adjusted manually (invariably reduced) to just exceed the noise level evident in the smoothed velocity trace. The slow phase velocity was calculated from the mean value in the velocity channel during each slow phase to give the (MSPV).

Figure 2.5. *On screen display of "Spike 2" file of torsional data analysis. A velocity threshold shown on channel B was used to determine saccades (channel A). The torsional OKN recording is shown in channel D. Torsional recording 'quality' is shown by channel C. The velocity threshold was adjusted manually (invariably reduced) to just exceed the noise level evident in the smoothed velocity trace.*



2.3. Torsional angular velocity

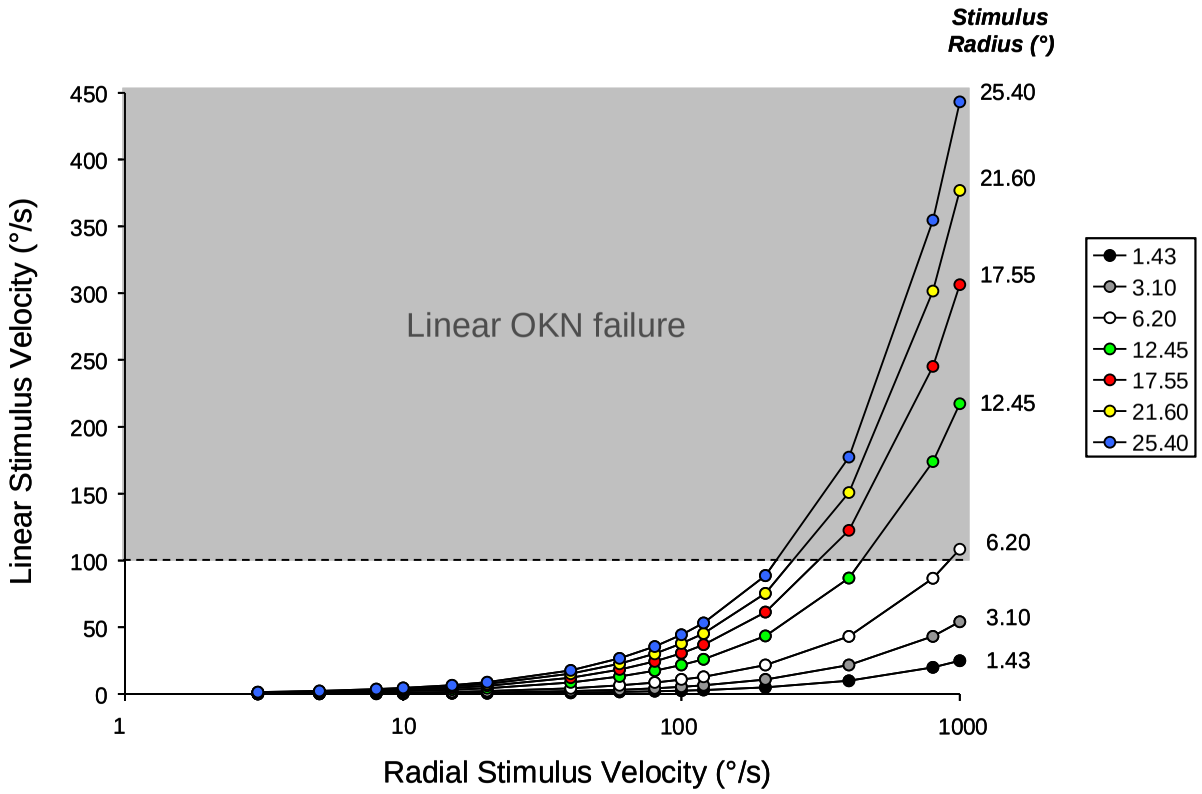
When referring to the rotational velocity of a torsional OKN stimulus, it is conventional to refer to the radial velocity, namely the angle the stimuli rotates through around the centre of the display per unit of time. This has also been used by previous authors to describe the velocity of tOKN stimuli (Collewijn *et al.*, 1985; Cheung & Howard, 1991; Morrow & Sharpe, 1993; Suzuki *et al.*, 2000). This method of stimulus speed, however, does not directly equate to the OKN velocity used to describe horizontal and vertical OKN stimuli. Although these are also described as rotational velocities (usually in degrees per second) they are defined with reference to visual angle (so for example a stimulus moving at 10°/s covers 10° of visual angle per second). Effectively the velocities describing horizontal and vertical OKN stimuli are linear velocities, since the stimuli are planar motion. To understand the relationship between the motion of the tOKN stimulus at different stimulus eccentricities to the linear velocities used to describe horizontal and vertical OKN, Table 2.1 shows the corresponding linear velocities for all radial velocities used in all experiments at different stimulus eccentricities.

Figure 2.6 shows a plot of the relationship between the radial stimulus velocity and the calculated linear velocity with increasing stimulus radius sizes. This shows that linear velocities associated with the faster radial velocities and greater eccentricities exceed that normally able to generate a robust horizontal or vertical response (i.e. linear velocities below 100°/s). For example, the linear OKN velocity exceeds 100°/s (shaded in yellow on table 2.1 and grey on figure 2.6) for stimuli of radial velocity of 400°/s (stimulus eccentricity (radius) of greater than 17.55º), 800°/s (stimulus eccentricity greater than 12.45º) and 1000°/s (stimulus eccentricities greater than 6.2º).

Stimulus Velocity (°/s)	3	5	8	10	15	20	40	60	80	100	120	200	400	800	1000
Stimulus Velocity (rad/s)	0.05	0.09	0.14	0.17	0.26	0.35	0.70	1.05	1.40	1.75	2.09	3.49	6.98	13.96	17.45
Radius (°)															
1.43	0.07	0.12	0.20	0.25	0.37	0.50	1.00	1.50	2.00	2.50	2.99	4.99	9.98	19.97	24.96
3.10	0.16	0.27	0.43	0.54	0.81	1.08	2.16	3.25	4.33	5.41	6.49	10.82	21.64	43.28	54.11
6.20	0.32	0.54	0.87	1.08	1.62	2.16	4.33	6.49	8.66	10.82	12.99	21.64	43.28	86.57	108.21
12.45	0.65	1.09	1.74	2.17	3.26	4.35	8.69	13.04	17.38	21.73	26.08	43.46	86.92	173.83	217.29
17.55	0.92	1.53	2.45	3.06	4.59	6.13	12.25	18.38	24.50	30.63	36.76	61.26	122.52	245.04	306.31
21.60	1.13	1.88	3.02	3.77	5.65	7.54	15.08	22.62	30.16	37.70	45.24	75.40	150.80	301.59	376.99
25.40	1.33	2.22	3.55	4.43	6.65	8.87	17.73	26.60	35.47	44.33	53.20	88.66	177.33	354.65	443.31

Table 2.1 *Linear stimulus velocity (°/s) with corresponding angular velocity (°/s) for all stimuli used in all experiments. Shaded Area in yellow shows the stimuli that exceeded linear velocity of 100 °/s.*

Figure 2.6. *Relationship between radial stimulus velocity against the calculated linear velocity at increasing size stimulus radius*



2.4. Methodological problems encountered

2.4.1. Aliasing

For experiment 1, investigating the effect of stimulus velocity on tOKN generation, the stimuli used to elicit the response originally consisted of a stimulus that included a sinusoidal grating pattern at a cycle size 30°, containing 12 radiating black and white stripes. This stimulus was found only to be suitable at slower stimulus velocities up to 120°/s due to counter rotational effects caused by aliasing. Aliasing is the distortion or artifact that results when a signal is sampled and reconstructed as an alias of the original signal. This affected experiment 1, looking at the effect of stimulus velocity on tOKN generation. Initially the projection rate of the stimulus at higher stimulus velocities was not adequate enough to match the rotational frequency of the stimulus, and therefore a distortion occurred making the stimulus appear to be rotating in the opposite direction due to the rate at which the stimulus is being sampled. To avoid this problem, a stimulus cycle size 90° containing four black and white sectors was used for the higher stimulus velocities beyond 120°/s.

2.4.2. Projector artifact

A further problem occurred with the original projector (Hitachi CP-X958) when projecting high velocity stimuli as a jerky projection of the stimulus occurred. This model of projector has two settings, the VGA setting which is of a high resolution setting but not suitable for moving images because it contains a motion artifact (resulting in a stuttering movement) and an S-Video setting that is of lower resolution but is able to deal with smooth motion. This S-Video setting is suitable for horizontal and vertical OKN stimuli as

these are at a lower spatial frequency and do not vary with eccentricity of the stimulus. For tOKN stimuli, a projection system was required that could provide smooth movement and high spatial frequencies. A new projector (model Epson EMP 703), capable of being used at a resolution of 1024x768 pixels resolution was purchased and subsequently used in all experiments. This delivered large spatial frequency stimuli at faster stimulus velocities which enabled a large range of stimulus velocities to be tested for experiment 1.

2.4.3. Strabs set-up (pupil size)

Setting up the 'Strabs' VOG system proved to be highly problematic due instability of torsional iris segment that was defined. Initially the camera setup as described in section 2.2 (p75) was performed while the subject was viewing a white screen with a black fixation target. This involved camera setup and arc selection and was done to satisfactory standards achieving good quality of greater than 0.5. However during the experiment the quality of the recording was severely impaired and so gave very noisy recordings. It was felt the altered illumination between camera set-up and viewing the tOKN stimuli may have caused enough of a difference in pupil size to impair tracking of the selected iris arc segment.

To combat this problem the infra-red cameras were set up while the subject viewed the centre of the stationary tOKN stimulus so that illumination levels were kept as close as possible to experimental conditions to avoid any pupil size change. Furthermore, subjects were instructed to keep the stimulus as clear as possible throughout testing so as maintain a constant pupil size.

2.4.4. Variable noise

During data analysis, the usual method of using a fixed velocity threshold to identify quick phases in the OKN trace had to be modified. The velocity threshold was able to be adjusted manually by the experimenter so that it was set above the level of system noise that was normally occurring in the 'Strabs' system. This enabled the researcher to identify quick and slow phases accurately. Visualisation of the torsional quality trace was also included in the analysis program to aid in correctly identifying fast and slow phases and not erroneously picking out sections that were simply poor quality data.

2.4.5. Blank phase for tOKAN

A blank phase (with no visual stimulation, i.e. black screen) was initially introduced in the experimental paradigm following stimulation of the tOKN stimulus to detect torsional optokinetic after-nystagmus (OKAN). This would give us more information regarding the nature and mechanism of the tOKN system as it is believed that a *delayed* system is said to contribute optokinetic after-nystagmus which is primarily subcortical in origin. Unfortunately, altered torsional eye quality resulted due to a change in illumination in this phase. This meant that torsional eye recordings were not of high enough quality to be able to detect any after-nystagmus with accuracy.

3. Experiment 1: The effect of stimulus velocity on torsional OKN generation.

3. Experiment 1: The effect of stimulus velocity on torsional OKN generation.

3.1. Procedure

The stimuli used for this experiment consisted of sinusoidal grating patterns subtending 50.8º in diameter. Stimulus velocities ranging from 3°/s to 1000°/s were used. The whole range of stimulus velocities was tested in three stages. Table 3.1 illustrates how the whole range of stimulus velocities was tested.

Table 3.1. *Stimulus velocities tested at each stage and volunteers tested*

Stage 1	
Stimulus: cycle size 30º	
Stimulus velocity °/s	3, 5, 8, 10, 15, 20
Subjects tested	1, 2, 3, 4, 5, 6, 7, 8
Stage 2	
Stimulus: cycle size 30º	
Stimulus velocity °/s	20, 40, 60, 80, 100, 120
Subjects tested	1, 3, 9, 10, 11, 12, 13, 14
Stage 3	
Stimulus: cycle size 90º	
Stimulus velocity °/s	20, 40, 100, 200, 400, 800, 1000
Subjects tested	1, 3, 15, 16, 17, 18, 19, 20

A sinusoidal grating pattern of cycle size 30°, containing 12 radiating black and white sectors, was used to investigate stimulus velocities between 3°/s and 120°/s

presented in a random order (stages 1 and 2 on Table 3.1). To limit counter-rotational stimulus projection aliasing effects, when using faster stimuli, a grating pattern of cycle size 90 ° containing four black and white sectors was used to investigate stimulus velocities between 20°/s to 1000°/s in a random order (stage 3 on Table 3.1). The subject was asked to fixate the stimulus binocularly. Each stimulus was presented for a period of 30 seconds in clockwise and anticlockwise directions, followed by a blank phase of 15 seconds consisting of a black screen. Up to 15 tests were done in one sitting. Eye movement recordings were taken as stated in section 2.2.

3.2. Data analysis

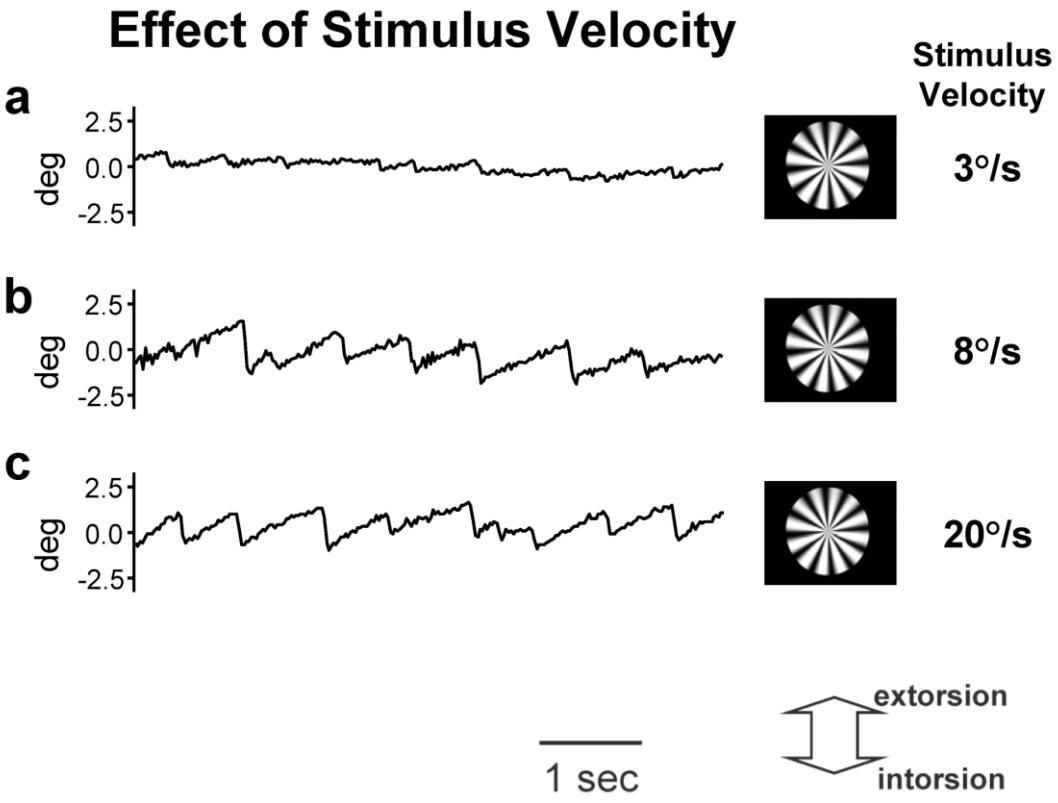
Since the mean slow phase velocities and gains were not normally distributed across subjects, medians and quartiles were used when representing the data in experiment 1 and 2. The correlation between MSPV and stimulus velocity was investigated using linear regression analysis.

3.3. Results

3.3.1. Original Data

Figure 3.1 shows original eye movement recordings obtained in one representative subject. Traces (a), (b) and (c) show original recordings acquired at 3°/s, 8°/s and 20°/s, respectively. While there is a small tOKN response at 3°/s, a clear response is demonstrated at 8°/s and 20°/s respectively. There were only two subjects out of eight who exhibited a visible tOKN response at 3°/sec in the clockwise direction and one subject displayed a response in the anticlockwise direction.

Figure 3.1. *Original recordings of the right eye from one representative subject showing the effect of stimulus velocity on torsional optokinetic nystagmus (tOKN). The stimulus rotating is rotating in the clockwise direction at 3º/s (a), 8º/s (b) and 20º/s (c).*



Most subjects showed a tOKN response when viewing the stimulus at 8°/s, with six subjects showing a response in the clockwise direction and five subjects in the anticlockwise direction. In total we recorded 8 subjects at all stimulus velocity ranges. The data was analysed and is illustrated in figure 3.2.

3.3.2. Analysis of gain

Figure 3.2 shows the median gain tOKN response plotted against log stimulus velocity in all subjects across all stimulus velocities in both clockwise and anticlockwise

directions. At stimulus velocities of 3°/s and 5°/s the median gain was zero. The largest gain occurred at 8°/s stimulus velocity in both clockwise and anticlockwise directions (gain = 0.16 and 0.13 for clockwise and anticlockwise stimulation, respectively). Between the stimulus velocities of 8°/s to 20°/s, the median gain varied from 0.16 to 0.08 and 0.13 to 0.07 for clockwise and anticlockwise stimulation respectively. When stimulus velocity was increased from 20°/s to 120°/s, the median gain fell to 0.03 for clockwise and anticlockwise stimulation respectively. At the highest stimulus velocity of 1000°/sec the gain fell to 0.002 and 0.0019 for clockwise and anticlockwise stimulation. There was no difference in gain between the 30° and 90° cycle size stimuli which were both tested at velocities of 20°/s, 40°/s, and 100°/s.

3.3.3. Analysis of slow phase velocity (SPV)

Even though tOKN gain decreased with increasing stimulus velocity the mean slow phase velocity (MSPV) actually increased as stimulus velocity increased up to 200°/s achieving a maximum MSPV of approximately 3°/s (gain= 0.015) in both directions. The relationship between stimulus velocity and the torsional response approximated to a linear correlation between the log of stimulus velocity and MSPV as shown in Figure 3.3.

For a cycle size of 30° (see left hand plots of 3.3 (a) and 3.3 (b)), the response commenced at 3.4°/s stimulus velocity for clockwise stimulation and 3.3°/s stimulus velocity for clockwise stimulation (intercept with the x-axis). The MSPV increased linearly by approximately 2°/s per log unit increase, up to the maximum stimulus velocity used of 120°/s (r^2 = 0.95 for clockwise stimuli and 0.93 for anticlockwise stimuli). For a cycle size of 90° (right hand plots of 3.3 (a) and (b)), the MSPV increased linearly by

approximately 1.5°/s per log unit increase from 20°/s to 200°/s. Above 200°/s, however, the MSPV began to tail off, decreasing to a MSPV of approximately 2°/s for maximum stimulus velocity used of 1000°/s (gain =0.002). For all velocities, there was no difference between clockwise and anticlockwise stimulation.

Figure 3.2. *Median torsional optokinetic nystagmus gain (± quartiles) in the clockwise and anticlockwise directions. Responses of all subjects in response to stimuli rotating at radial stimulus velocities from 3/s to 1000º/s*

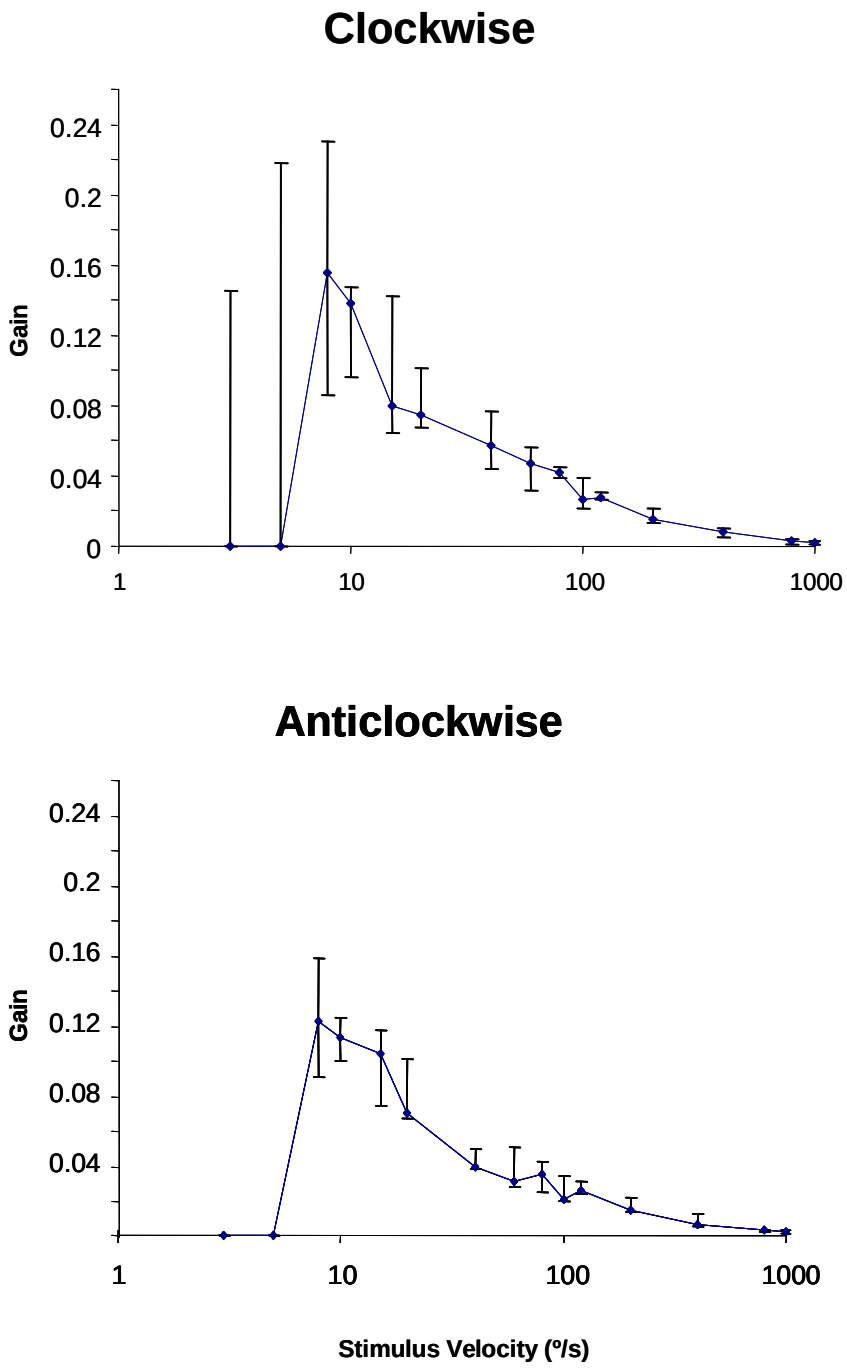
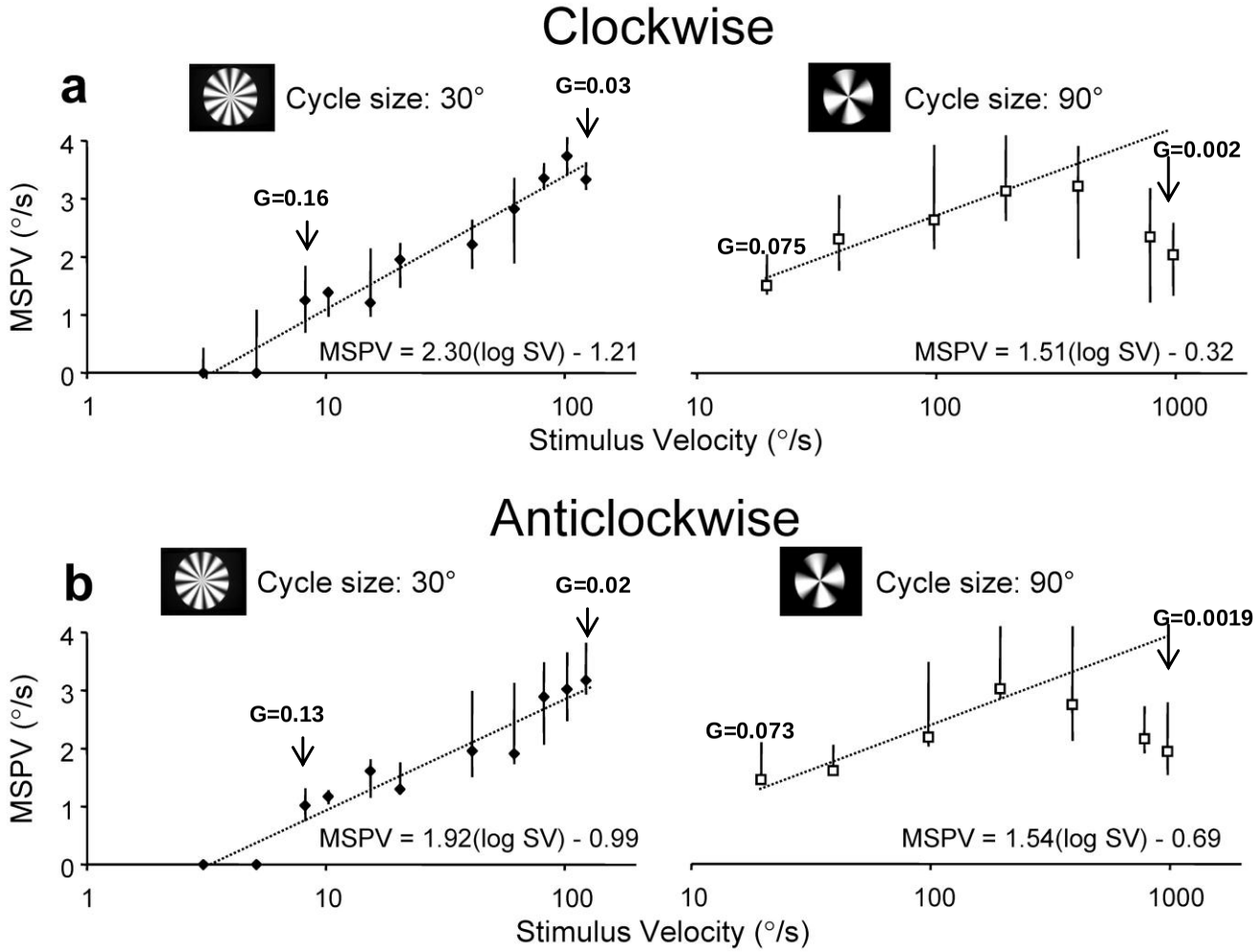


Figure 3.3 *Mean slow phase velocity (median ± quartiles) of all subjects in relation to the log of the stimulus velocity for stimulus velocities ranging from 3°/s-120°/s at cycle size of 30° (left hand plots of a and b), and stimulus velocities ranging from 20°/s-1000°/s at cycle size of 90° (right hand plots of a and b), to clockwise and anticlockwise stimulation The arrows labelled 'G' refer to the gain value at that point.*



3.3.4. Discussion

This study demonstrates a significant, previously unreported relationship between the tOKN mean slow phase velocity (MSPV) and stimulus velocity. We found that the MSPV is linearly related to the log of the stimulus velocity, displaying no difference in either clockwise or anticlockwise stimulation.

The maximum gain occurred in response to 8°/s stimulation with median values of 0.16 and 0.13 in clockwise and anticlockwise directions, respectively. Previously reported values in response to similar stimulus velocities differ greatly. Collewijn *et al*.(1985) report a very low gain value of 0.035 to 6°/s tOKN stimulation in two subjects with highly variable results, compared to the higher value of 0.22 reported by Morrow *et al*. (1993) in response to 10°/s stimulation. The cause of such disparity in gain reported previously could be due to differences in the stimuli used to generate tOKN. Random dot pattern was employed by Collewijn *et al*.(1985), whereas radiating stripes, similar to that used in the present study were used by Morrow *et al.* (1993). When reviewing previous papers, studies employing a random pattern stimulus to measure torsional optokinetic nystagmus tended to show peak gain of less than 0.1 (Collewijn *et al.*, 1985; Cheung & Howard, 1991; Suzuki *et al.*, 2000), whereas studies using radiating stripes of various forms (with the exception of one study (Seidman *et al.*, 1992)) report peak gain responses of greater than 0.1 (Morrow & Sharpe, 1993; Howard *et al.*, 1994; Thilo *et al.*, 1999). Therefore, radiating stripes due to their regular pattern may be best suited to tOKN generation.

Our results also demonstrate a measurable tOKN response at a higher range of stimulus velocities than previously reported with tOKN being elicited when the stimulus rotated as fast as a radial velocity of 1000°/s achieving a gain of 0.0020 and 0.0019 for

clockwise and anticlockwise directions, respectively. It was also interesting to note that even though tOKN gain decreased with increasing stimulus velocity, the mean slow phase velocity (SPV) actually increased as stimulus velocity increased up to 200°/s achieving a maximum mean SPV of approximately 3°/s in both directions. Previous papers (Collewijn *et al.*, 1985; Cheung & Howard, 1991; Seidman *et al.*, 1992; Morrow & Sharpe, 1993; Suzuki *et al.*, 2000) have not used a large enough stimulus velocity range to establish which stimulus velocity elicited the peak response. It is possible that the excessive linear velocities generated at the periphery of the faster rotating stimuli limit any further increase in tOKN MSPV response (see section 2.3, page 81).

The capacity of the tOKN response in being able to be stimulated by very high velocities may be a feature that differentiates it from OKN in the horizontal and vertical directions. Previous reports show the SPV begins to decline from 80–90°/s stimulation in horizontal OKN (Holm-Jensen & Peitersen, 1979) and the gain has been reported to be low and irregular from 60°/s in vertical OKN (Wei *et al.*, 1992). The neural processes involved could explain the difference between OKN in the horizontal and vertical direction and that elicited in the torsional direction. There are two complimentary mechanisms involved in the generation of OKN in the horizontal and vertical directions. In humans, at slower stimulus velocities, a pursuit related mechanism is thought to mainly track the OKN stimulus which relies on central foveal fixation. A delayed OKN system also contributes to human OKN especially at the higher stimulus velocities and it is a system dominated more by peripheral vision (Howard & Ohmi, 1984; Wei *et al.*, 1992). Torsional OKN, by definition, is not influenced by a pursuit mechanism since little or no target movement takes place at the fovea when the subject fixates on target centre (Thilo *et al.*,

1999). This probably allows a purely reflexive OKN system to respond over a wide range of stimulus velocities, which is particularly suited to faster, peripheral stimulation.

4. Experiment 2: The effect of central and peripheral stimulation on tOKN generation.

4. Experiment 2: The effect of central and peripheral stimulation on tOKN generation.

4.1. Procedure

To measure the effects of central stimulation, the entire field of stimulation was varied from 2.86° to 50.8° in seven steps in a random order, described in Table 4.1. To assess varying degrees of peripheral stimulation on the tOKN response, an artificial central scotoma (black round spot) was incorporated in the stimulus projection to occlude its central portion. Table 4.2. shows the sizes of stimulus and subjects used. The occluder was varied in size from 2.86° to 43.2° presented in random order to eight normal volunteers (See ***Movie C, clips 3 and 4*** in *additional addenda CD*).

Table 4.1 *Testing of increasing size central field*

Central stimulation

Stimulus: cycle size 90º

Stimulus velocity º/s	40, 400
Field size (º)	2.86, 6.2, 12.4, 24.9, 35.1, 43.2, 50.8
Subjects tested	1, 2, 3, 4, 5, 6, 9, 12

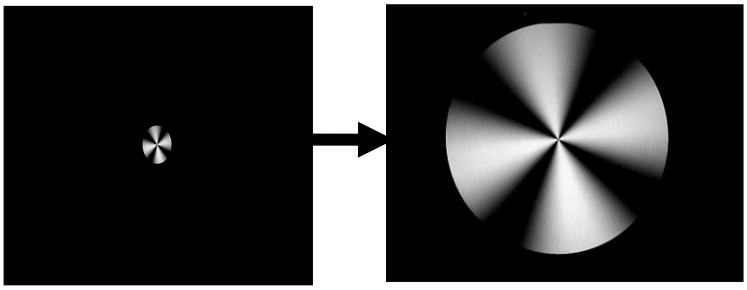
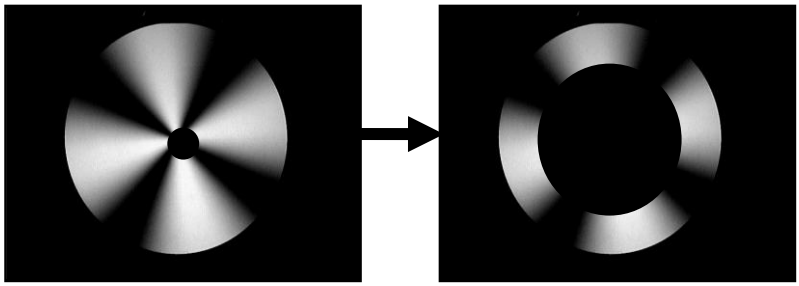


Table 4.2. *Testing of increasing size central occluder*

Peripheral stimulation
Stimulus: cycle size 90º

Stimulus velocity °/s	40,400
Occluder size (º)	2.86, 6.2, 12.4, 24.9, 35.1, 43.2
Subjects tested	1, 2, 3, 4, 5, 6, 9, 12



A response box was used by the subjects to indicate when they 'filled- in' the missing central portion of the stimulus (Cambridge Research Systems, Rochester, UK) (See ***Movie C, Clip 4*** *in additional addenda CD* to perceive *filling- in* effect). All tests consisted of a 30 second binocular stimulation period followed by a blank phase as in experiment 1. The effects of central and peripheral stimulation were measured at velocities of 40°/s and 400°/s.

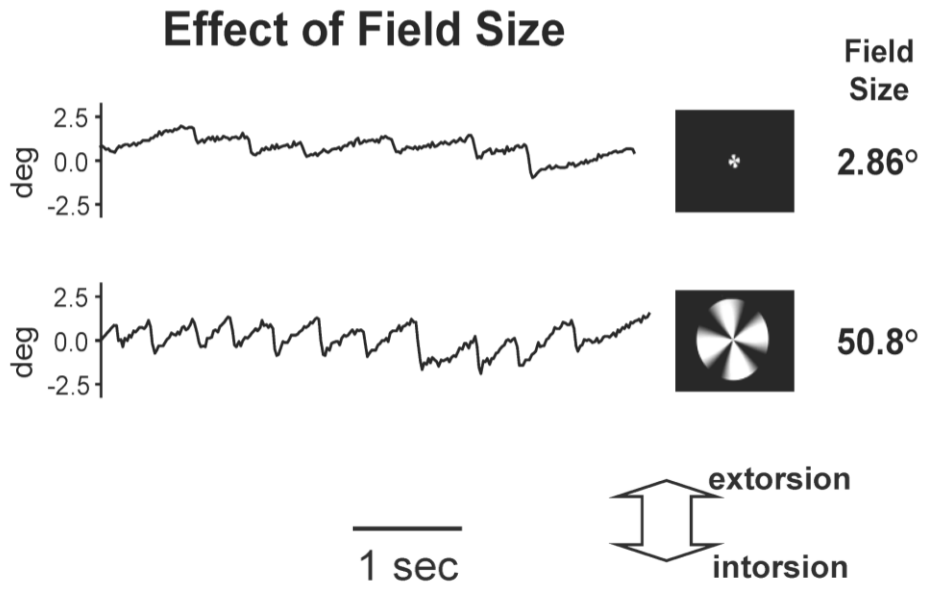
4.2. Results

4.2.1. Original Data: Increasing stimulus field size

Figure 4.1. shows original recordings of one representative subject obtained with stimulus field size of 2.86° and 50.8° at 40°/s clockwise stimulation, displaying an

increased magnitude of response to the larger field size (50.8º). In total, recordings from eight volunteers were taken. The combined results are displayed in Figure 4.4.

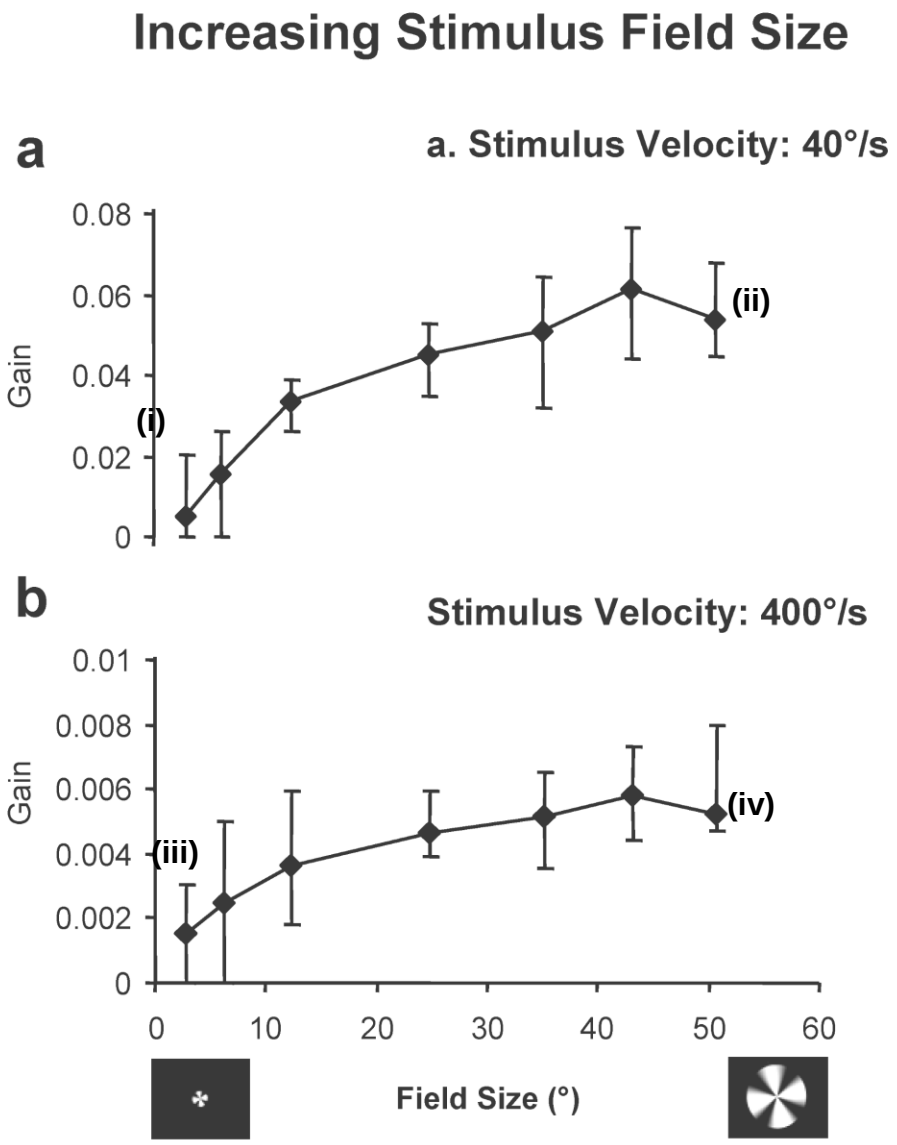
Figure 4.1. *Original recordings of the right eye from one representative subject showing the effect of increasing stimulus field size on torsional optokinetic nystagmus (tOKN).*



4.2.1.1. Analysis of gain

Figures 4.2 (a) and (b) show that with increasing stimulus field size, the median tOKN gain increases at 40 and 400°/s. The smallest field size of 2.86°, rotating at 40°/s (Label (i) on Figure 4.2 (a)) resulted in only 10% (0.0054) of the gain elicited by the largest field display of 50.8° (0.054) (Label (ii) on Figure 4.2 (a)). At 400°/s, (Label (iii) Figure on 4.2 (b)) the gain elicited to the smallest field size was 29% (0.0015) of the gain obtained by the largest stimulus (0.0052) (Label (iv)).

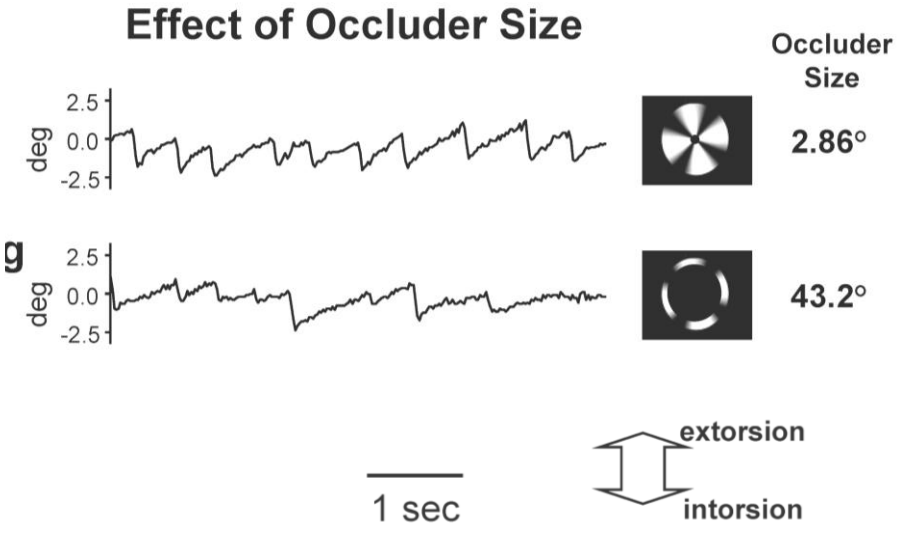
Figure 4.2 *Median torsional optokinetic nystagmus gain (± quartiles) of all subjects in response to increasing stimulus field size with the stimulus rotating at (a) 40º/s and (b) 400º/s in the clockwise direction.*



4.2.2. Original Data: Increasing size central occluder (peripheral stimulation).

Figure 4.3 shows original recordings obtained with the smallest (2.86°) and largest central occlusion (43.2°). The tOKN response is found to be present even when 85% of the stimulus was occluded. The stimulus is rotating at 40°/s. In total, recordings were taken from eight normal volunteers. The combined results after analysis of all subjects are displayed in Figure 4.4.

Figure 4.3. *Original recordings of the right eye from one representative subject showing the effect of increasing central occluder size on torsional optokinetic nystagmus (tOKN).*



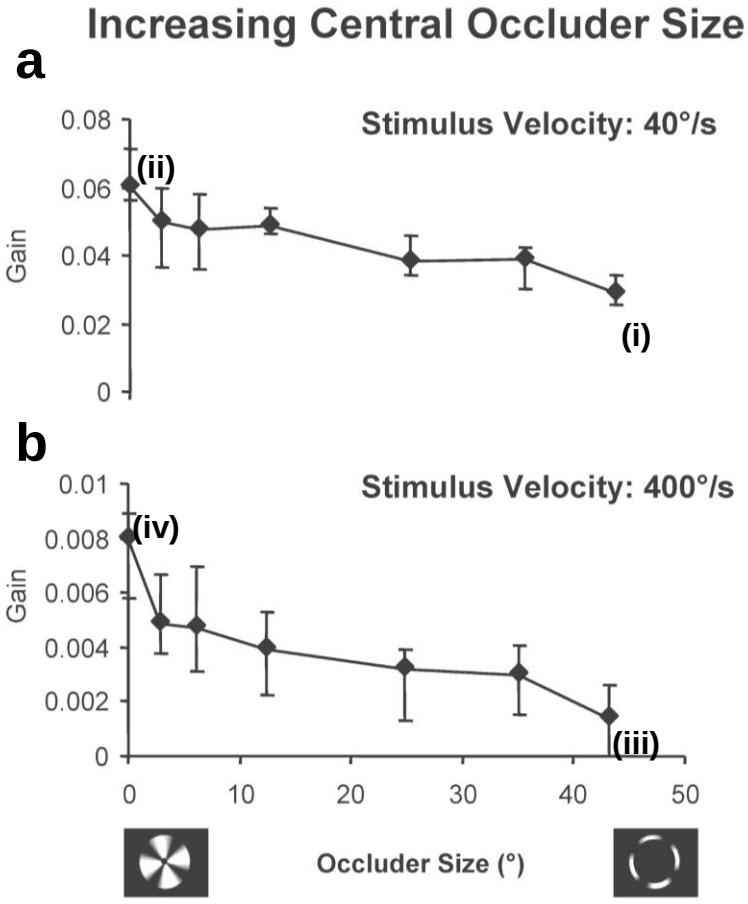
4.2.2.1. Analysis of gain.

Figures 4.4 (a) and 4.4 (b) illustrate the effect of increasing central occluder size on median tOKN gain at the two different stimulus velocities used.

At label (i) on Figure 4.4 (a), 85% of the 50.8° display is occluded, leaving only a peripheral stimulus. When this occurred at 40°/s, the gain was half (0.03) of the gain evoked when no central occluder was used (0.06 (label (ii) Figure 4.4 (a)).

At 400°/s, shown on Figure 4.4 (b), using the largest central occluder, label (iii), the gain was 17.5% (0.0014) of the gain evoked without any central occlusion, label (iv), 0.0080).

Figure 4.4 *Median torsional optokinetic nystagmus gain (± quartiles) of all subjects in response to increasing central occluder size with the stimulus rotating at (a) 40º/s and (b) 400º/s in the clockwise direction.*



4.2.3. Comparison of stimulus area in relation to linear stimulus velocity.

Figure 4.5 shows the combined results of experiments with increasing stimulus field size and increasing size central occluder at radial velocities of 40º/s and 400º/s with corresponding linear velocities. For the increasing field size experiment, shown by (a) and (b) on figure 4.5, corresponding linear stimulus velocity is shown at the most peripheral point of the stimulus.

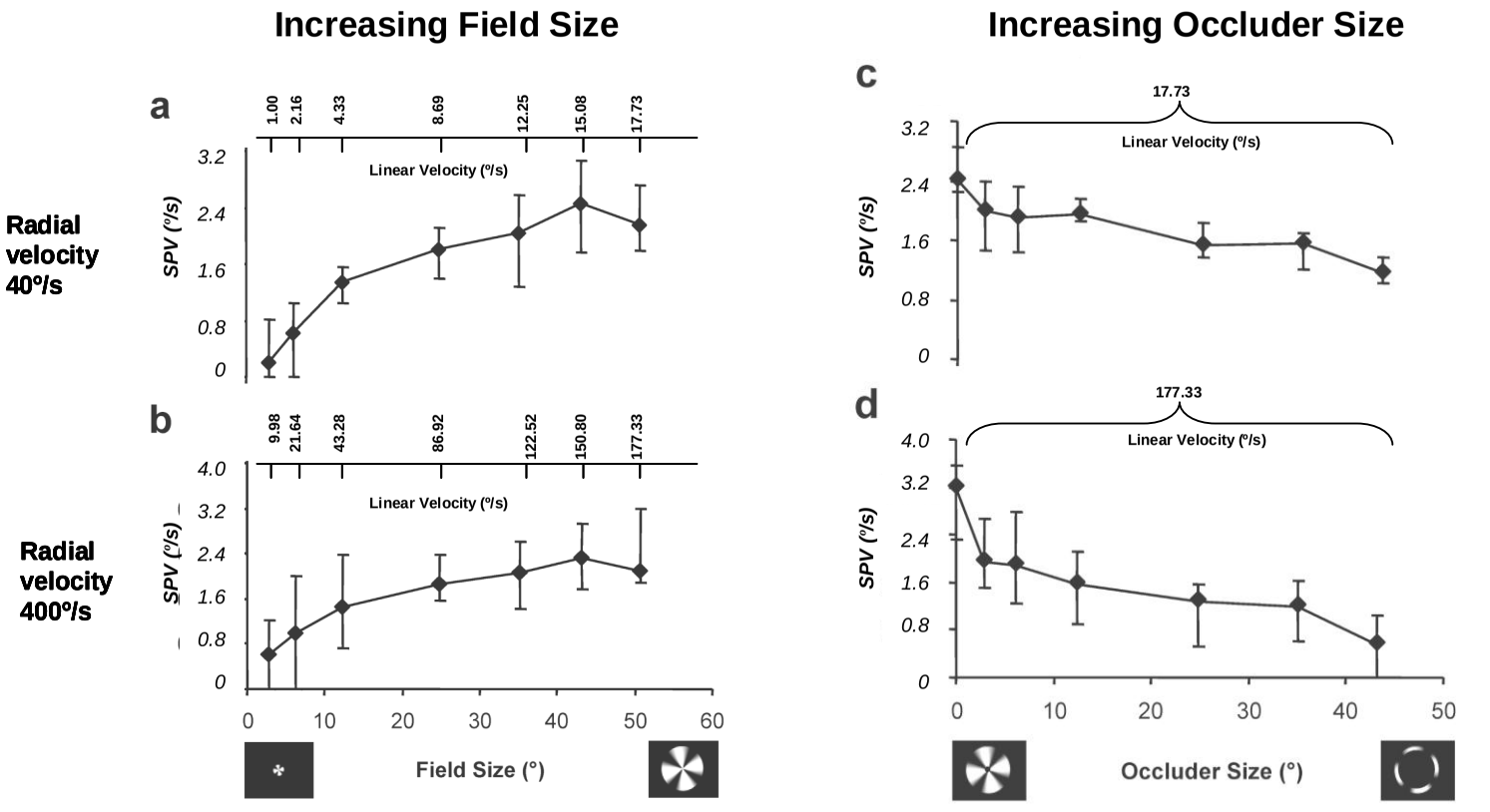
For 40º/s, the smallest field size (peripheral stimulus linear velocity =1.00º/s) elicited an eye velocity of 0.22 º/s. The largest field size (peripheral stimulus linear velocity = 17.73º/s), elicited a SPV of 2.16 º/s.

At the radial velocity of 400º/s, the smallest field size (peripheral linear velocity = 9.98º/s) elicited an eye velocity of 0.6º/s. The largest field size (peripheral linear velocity = 177.33) elicited a SPV of 2.08º/s.

Figure 4.5 (c) and (d) shows comparison to the central occluder experiments. The peripheral linear stimulus velocity = 17.73º/s (radial velocity = 40º/s) elicited a SPV of 1.2º/s at the largest central occlusion compared to 2.4º/s when no central occluder was used.

At the radial velocity of 400º/s, (peripheral linear stimulus velocity: 177.33º/s) the SPV elicited was 0.56º/s at the largest central occlusion and 3.2º/s when no occlusion was used.

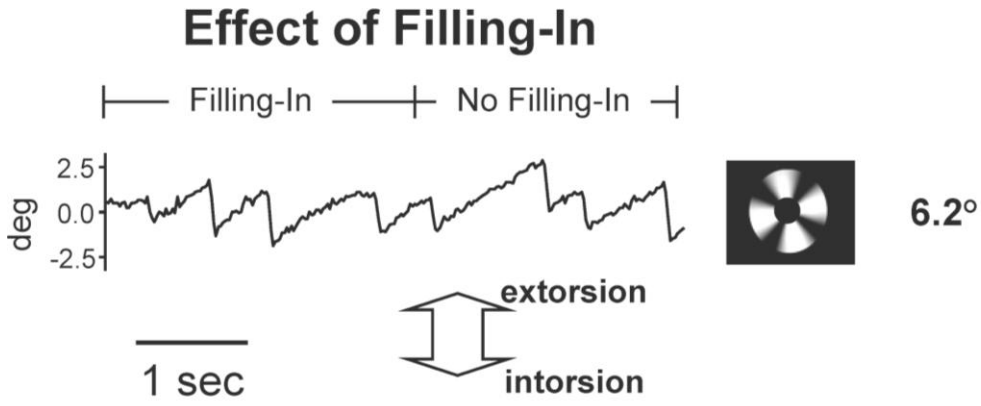
Figure 4.5 *Combined results of tOKN slow phase eye velocity (SPV) ± quartiles for experiments with increasing stimulus field size and increasing size central occluder at radial velocities of 40°/s and 400°/s. Linear velocities at the most peripheral point of the stimulus are also shown.*



4.2.4. Effect of Filling-in

During the central occlusion experiments, several subjects reported 'filling-in' of the centrally occluded area by perceiving the continuation of the stripes of the stimulus into the central occluded area (see *movie C, clip 4*). The perception of filling-in was changeable with some subjects constantly perceiving filling-in and others fluctuating between filling-in being present and absent within the 30 second period of stimulation. Figure 4.6 shows a sample of eye movement recording trace where filling-in and no filling-in are indicated during the same period of stimulation. There are no differences in waveform during the two conditions.

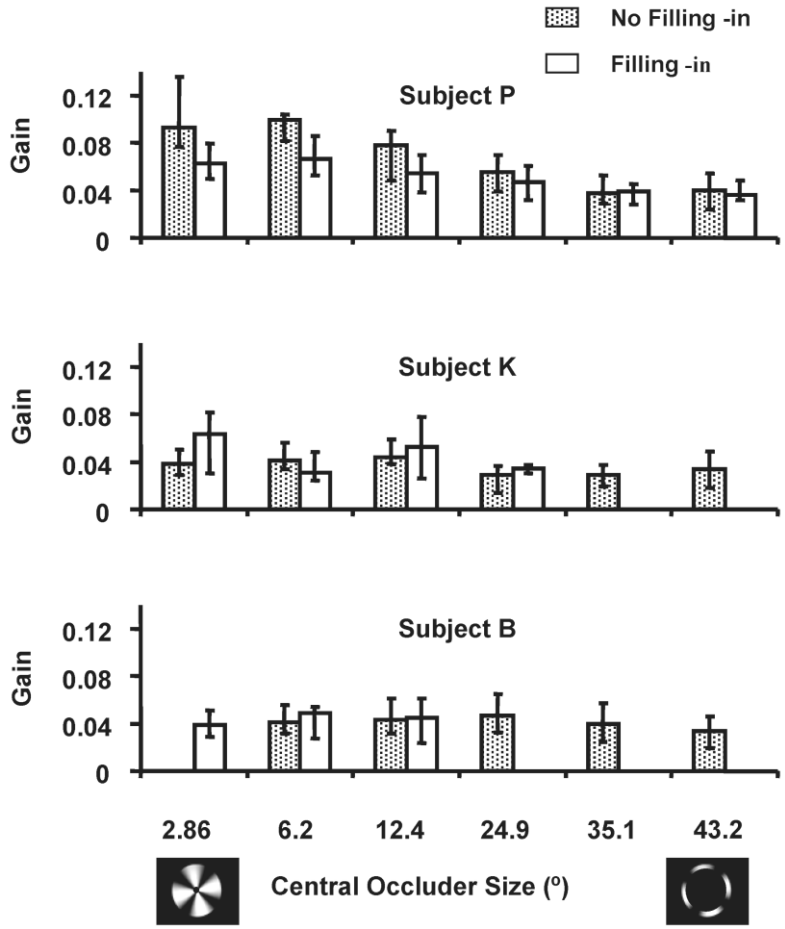
Figure 4.6. *Original recordings of the right eye showing the effect of filling-in with the stimulus rotating in the clockwise direction at 40°/s.*



The eye movements of three subjects who reported this perception were examined in detail to investigate whether this perception had any effect on the eye movements generated. The central occlusion experiments were repeated three times in the three subjects at a stimulus velocity of 40°/s. Figure 4.7 shows the tOKN gains during filling-in

and none filling-in periods of the peripheral stimulus in all three subjects. All subjects consistently demonstrated a filling-in response at the smaller sized central occluders of 2.86°, 6.2° and 12.4° at both stimulus velocities. There was no visible difference in tOKN gain when subjects filled-in the stimulus to when they did not.

Figure 4.7. *Changes in torsional optokinetic nystagmus gain during periods of filling-in and no filling-in as central occluder increases in size with the stimulus rotating at 40º/s, in three subjects. Where only one bar is present, this indicates either filling-in or no filling-in for the whole period tested.*



4.3. Discussion

We have shown that peripheral field stimulation contributes to a large proportion of the tOKN response, in contrast to previous reports, which state that the response is mainly dependent on central field stimulation (Howard *et al.*, 1994). A 'filling-in' response was also reported in subjects when central areas of the stimulus were occluded but did not influence the OKN response.

The results of our investigation into stimulus area and tOKN gain, suggest that peripheral field stimulation contributes to a large amount of the tOKN response. In our experiments, the smallest field size display evoked only a small proportion of the gain (10% at 40°/s) elicited by the largest field stimulus. We have also demonstrated that when a large amount (43.2°) of the central field was occluded a considerable amount of the tOKN gain was retained (50% at 40°/s).

4.3.1. How does this compare to previous work?

The only previous study performed, (Howard *et al.*, 1994) investigating the effects of central and peripheral stimulation on the tOKN response, concluded that tOKN had a preference for centrally placed stimuli. This was based on the assumption that when the central 75° of their display was occluded only 30% of the full field tOKN response was maintained. The normal binocular field is approximately 120° in total in the horizontal direction and 135° in the vertical direction (Henson, 1998). In view of this, 75° actually represent a large proportion of the total binocular visual field including a significant amount of the peripheral field. Therefore, 30% of the tOKN response being retained

demonstrates a remarkable capacity of the tOKN system, to be stimulated by the peripheral field alone.

4.3.2. Importance of peripheral field

The importance of the peripheral field could also be related to the degree of linear slip of the tOKN stimulus in relation to the area of retina stimulated. This is because tOKN generation depends on the image slip rotating around the central retina, and the amount of image slip increases, the further the stimulus is presented away from the central retina (Morrow & Sharpe, 1993). Further evidence to support the significance of peripheral vision on OKN generation comes from studies investigating patients with pathological loss of central vision. Abadi *et al*., (1997) and Valmaggia *et al,*. (2002) have demonstrated that patients with central scotomas, due to age related macula degeneration, do not show any reduction in horizontal OKN gain. It is still unknown whether OKN gain is affected in the vertical and torsional directions in patients with pathological central scotomas. This would be an interesting avenue for further investigations.

4.3.3. Filling-in significance

Subjects in our study reported a perception of completion of the peripheral stimulus into the centrally occluded area, which was more apparent when the smallest sized central occluders of 2.86°, 6.2° and 12.4° were used. This process of 'filling-in' causes visual stimuli to be perceived as arising from an area of the visual field where there is no actual visual input (Safran & Landis, 1999). Filling-in of the peripheral stimulus did not have any measurable effects on the eye movements generated. This perception has not been

previously described in tOKN stimuli. However, Valmaggia & Gottlob (2002) have described a filling-in response occurring in horizontal OKN in patients with central scotomas of 15°, 18° and 16°. They observed that the filling-in elicited horizontal OKN eye movements whereas OKN was not present when there was no filling-in. The authors suggested that the ability of the filling-in to directly affect eye movements is the result of motion sensitive areas of the visual cortex being stimulated through the active neural adaptation processes that are triggered during filling-in (Valmaggia & Gottlob, 2002).

When artificial central scotomas are presented to normal subjects, as in our study, there might be no such neural adaptation taking place. The subjects used in our study have an essentially normal visual system but other active processes may be occurring to elicit the perceptual filling-in response. The absence of any significant effect on the eye movements generated during the filling-in response could also be related to the relatively small influence of the central field on tOKN. In our experiments filling-in produced a perception of the stimulus being present in central areas. Having shown that central stimulation alone evokes only a small proportion of the tOKN response, this could explain why we found no difference during periods of filling-in and no filling-in.

5. Experiment 3: The effect of aging on tOKN generation

5. Experiment 3: The effect of aging on tOKN generation

5.1. Procedure

A rotating sinusoidal grating pattern of 90º cycle size subtending 50.8 º in diameter was projected onto a rear-projection screen as the experimental stimulus. The stimulus revolved around its central axis at 40º/s and 400º/s in clockwise and anticlockwise directions. The volunteers were asked to stare at the stimulus keeping it in focus. Each stimulus was presented for 30 seconds followed by a blank phase of 15 seconds in which the subject was asked to fixate a black screen.

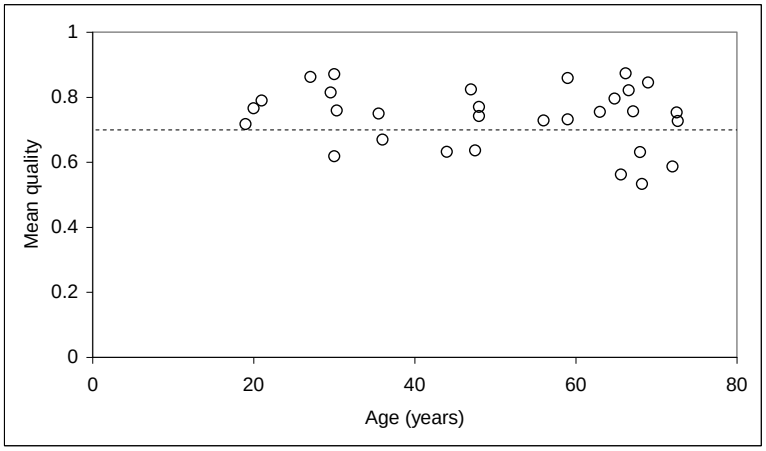
Recordings were taken monocularly and a cover was used to cover the non-viewing eye during testing. Responses from the right eye were recorded, unless VA was less than 6/9 (20/30) or eye movement recording quality was lower than 0.5, in which case the left eye was used (n=3).

Four of the subjects who showed no responses at 40º/s and 400º/s (all male and aged 56, 59, 63 and 72 years) were tested across a wider range of stimulus velocities, i.e. radial velocity of 20º/s, 100º/s, 200º/s, 800º/s and 1000º/s in both directions. As monocular eye-movement recordings were performed, the relative direction of rotation of the eye differed according to the fixing eye (i.e. clockwise stimulation to the right eye produces a slow phase that extorts the right eye and intorts the left eye and vice versa for anticlockwise stimulation). To avoid misinterpretation, the direction of the eye rotation and the velocity of the stimulus were defined in relation to intorsion/extorsion of the viewing monocular eye.

A drop in torsional quality of the data in the blank phase due to changing pupil size meant that measurement of torsional optokinetic after-nystagmus was unreliable.

Figure 5.1 demonstrates the mean torsional quality versus age. The quality of the torsional data during measurement of tOKN was found not to significantly change with age in the study (linear regression: r^2=0.02, p=0.2).

Figure 5.1. *Mean torsional quality in each volunteer versus age with the data line indicating a torsional quality of 0.7.*



5.2. Data analysis

For volunteers classified as responders, the mean velocity over a minimum of 10 slow phases from each 30-second trace was used to give the mean slow phase velocity (MSPV) for each stimulus. Since the mean slow phase velocities were not normally distributed across the subjects, median values were used for analysis. Volunteers classified as non-responders had no slow phases within any of the 30- second analysis section. One subject was excluded from the original study group of 31 subjects because the quality trace of the torsional segment fluctuated during testing so a constant noise free recording was difficult to achieve.

5.2.1. Statistics

(i) Changes in the proportion of non-functional tOKN with age were analysed using logistic regression. The odds ratio, in this analysis, was used to estimate the risk of being a non-responder with age.

(ii) The correlation between MSPV and age in volunteers who showed measurable responses was also analysed using the simple linear regression (Pearson's product-moment correlation coefficient).

5.3. Results

5.3.1. Original Data

Examples of original eye movement recordings are displayed in Figure 5.2 showing monocular eye movement recordings from a 21 year old subject (Figure 5.2 (A)), a 58 year old subject (Figure 5.2 (B)) and a 72 year old subject (Figure 5.2 (C)) at 400º/s stimulation in both rotational directions. Figure 5.2 (A) shows the 21 year old subject to have a clear tOKN response with slow phase in extorsion and intorsion directions displaying no real difference in response. Figure 5.2 (B) shows the 58 year old subject to have a diminished tOKN response in both rotation directions. In Figure 5.2 (C), the 72 year old male shows some fluctuations in torsion but this does not resemble any tOKN response.

5.3.2. Correlation between age and tOKN response

Figure 5.3 shows the correlation between age in years and MSPV in the intorsion and extorsion directions of all subjects at stimulus velocities of 40º/s (Figure 5.3 (A)) and

400º/s (Figure 5.3 (B)). The number of non responders (indicated with open circles and crosses for extorsion and intorsion, respectively) clearly increases with age.

Figure 5.2. *Original eye movement recordings of a 21 year old subject (A), a 58 year old subject (B) and a 72 year old subject (C) at 400º/s stimulation. A slope downwards indicates the eye making a slow phase in the extorsion direction and a slope upwards indicates an eye movement in the intorsion direction. Original data was smoothed using a 5-point boxcar filter.*

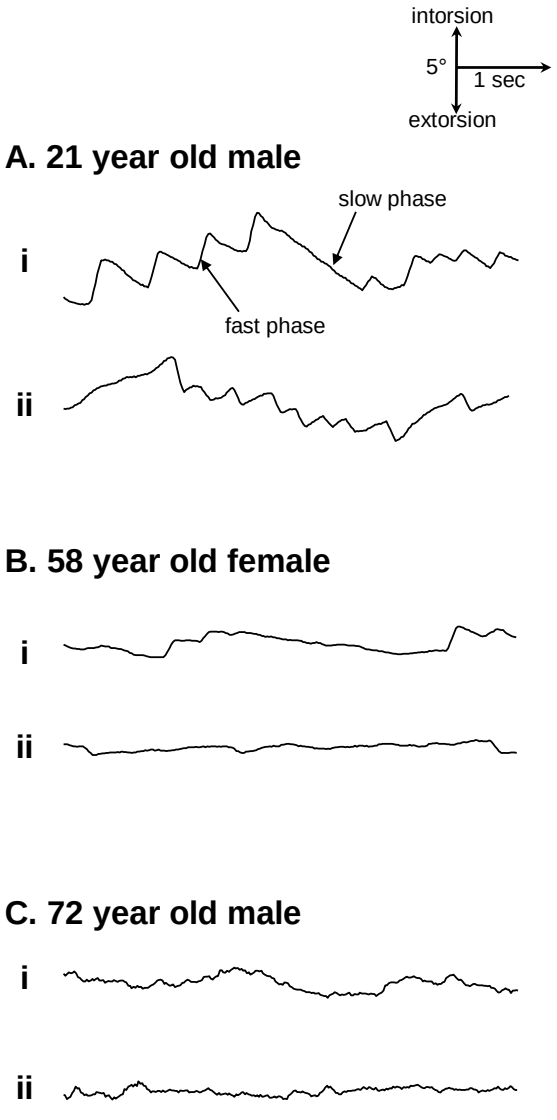


Figure 5.3. *Scatter plots of mean slow-phase velocity in (º/s) versus age in years at (5.3(A)) 40º/s and (5.3(B)) 400º/s stimulation. Responders and non-responders are distinguished (see legend). The grey dotted line is an estimate of the level at which* ***tOKN*** *can be detected.*

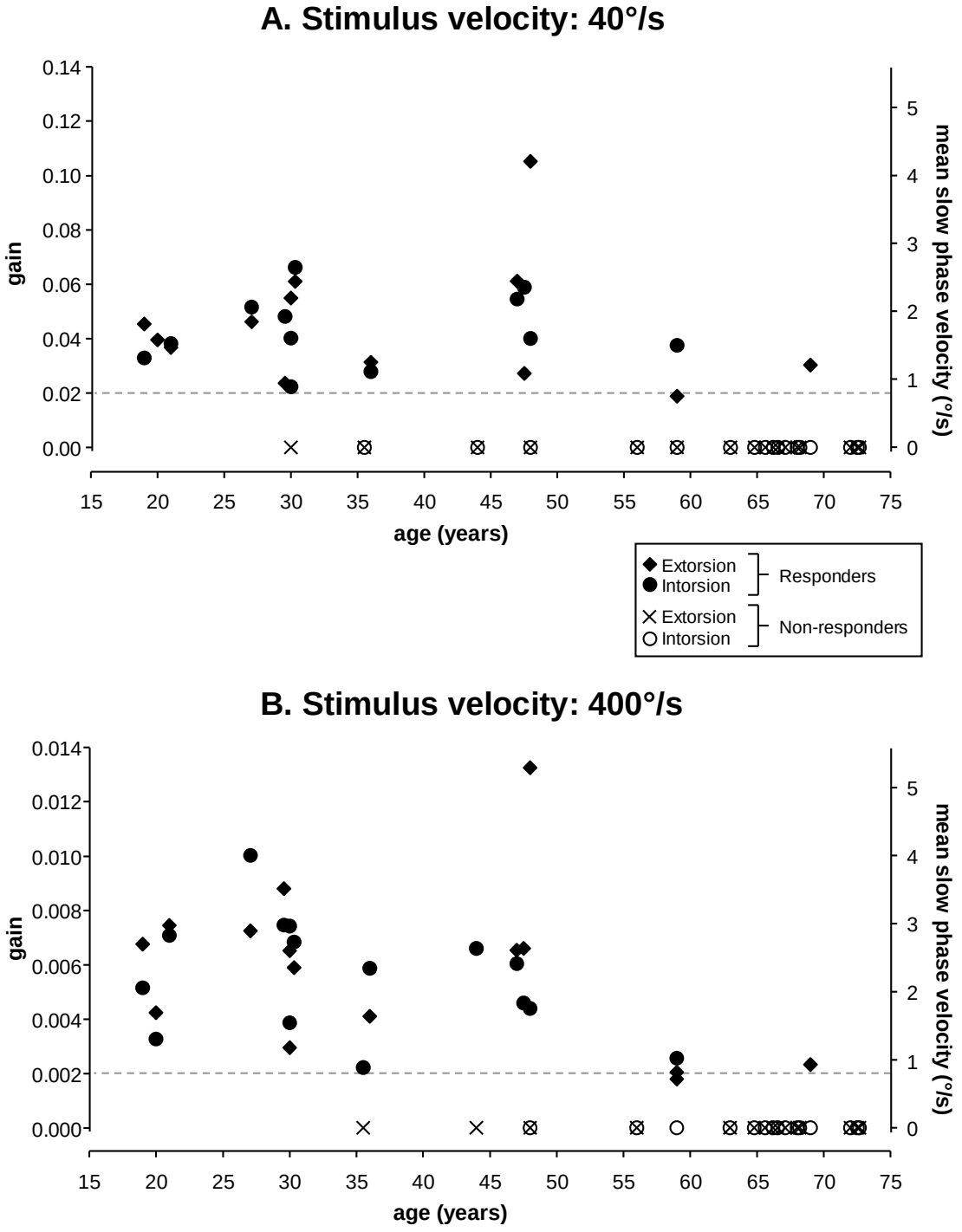


Table 5.1 shows significance levels (*p)* and the odds ratio after performing logistic regression. A significant change with age for stimulus rotations of 40º/s and 400º/s was found.

Table 5.1. *Significance levels (p) and odds ratio with 95% confidence Interval (CI) for change of torsional OKN with age using logistic regression.*

Direction	Velocity (º/s)	*p*	Odds ratio, (95% CI)
Extorsion	40	0.0029	0.91 (0.86 to 0.97)
Intorsion	40	0.0023	0.90 (0.84 to 0.96)
Extorsion	400	0.0026	0.90 (0.84 to 0.96)
Intorsion	400	0.0108	0.76 (0.61 to 0.93)

The odds ratio allows us to infer that for every year increase in age there was a 9.0% and 10.0% *risk* of not responding to tOKN stimuli at 40º/s, and a 10.3% and 24.3% *risk* of not responding to tOKN stimuli at 400º/s in extorsion and intorsion directions, respectively. Volunteers were split into the following age brackets: 19-40 yrs (n=10, median age 30, range 19-36), 41-65yrs (n=10, median age 52, range 44-65) and >65 yrs, (n=10, median age 68, range 66-72). The number of responders (i.e. volunteers who showed at least one response to stimuli in any direction of rotation at either stimulus velocity) were 10 out of 10 for 19-40 years, 6 out of 10 for 41-65yrs and 1 out of 10 for >65 yrs.

Simple linear regression was used to investigate change in mean slow phase velocity with age on volunteers that displayed a measurable response (i.e. excluding zero values). The results of this analysis were not significant for either 40°/s stimulation

(r=0.16, p=0.6 and r=-0.050, p=0.88 in extorsion and intorsion directions, respectively) or 400°/s (r=-0.33, p=0.23 and r=0.34, p=0.22).

5.3.3. Testing additional stimulus velocities.

Additional stimulus velocities of 20º/s, 100º/s, 200º/s, 800º/ and 1000º/s were tested in the four older volunteers (aged 56, 59, 63 and 72 years) tested at further stimulus velocities the volunteers aged 63 and 72 years demonstrated no detectable response when eye movement traces were analysed across all stimulus velocities. The 56 year old subject only responded at the stimulus velocity of 20º/s, in the anticlockwise direction, with a MSPV of 0.88º/s. The 59 year old subject responded at stimulus velocities of 200º/s in the clockwise direction and 20º/s in the anticlockwise direction with MSPV of 1.04º/s and 0.7º/s, respectively.

5.4. Discussion

This study shows for the first time that torsional optokinetic nystagmus is affected by aging. This effect was consistent over two stimulus velocities and occurred at approximately the same rate in extorsion or intorsion directions.

5.4.1. How does this compare to previous work?

In a prospective cross sectional study (249 subjects from the age ranges 18 days to 89 years), horizontal OKN mean gain has been shown to undergo a small but significant decline beyond 50 yrs of age (Valmaggia *et al.*, 2004). This is in agreement with other studies comparing a population of younger subjects and older subjects with superior

horizontal OKN gains always observed in the younger age group category (Spooner *et al.*, 1980; Simons & Buttner, 1985; Kato *et al.*, 1994). Similarly, vertical OKN was also reduced in healthy elderly subjects (mean age of 70±8 years) with lower tracking gain and greater phase lag in comparison to young normal subjects (mean age 30±6 years) (Demer, 1994).

The contrasting feature in our results to previous studies on horizontal and vertical OKN, however, is that the torsional OKN response is virtually undetectable in the elderly with only 1/10 subjects demonstrating a response in the age group category of above 65 yrs (median age= 68). The lack of response in the older volunteers was also consistent when other stimulus velocities were used to assess the tOKN response in four subjects that originally did not respond to stimuli rotating at 40°/s or 400°/s. Two older subjects, aged 63 and 72 years, did not show any response to other stimulus velocities, while two younger volunteers aged 56 and 59 showed minimal responses to stimuli rotating at 20°/s and 200°/s. Although previous studies show reduced horizontal and vertical OKN gain in the elderly, a response is still evident.

Possible explanations for these changes occurring with age could be the fact that the torsional OKN response has a very small gain with stimuli up to 200°/s yielding a maximum response of approximately 3°/s (Farooq *et al.*, 2004) as shown in experiment 1. Stimulus velocities of 40º/s and 400º/s were considered suitable for use as these had previously elicited a good response that was easily differentiated from the normally occurring noise in the recording (Farooq *et al.*, 2004). However, it is possible that torsional OKN responses are much closer to threshold compared to horizontal and vertical OKN making them more sensitive to aging processes. Another possibility is that torsional OKN

responses are present in the elderly but fall below the level of system noise. In general, videooculography yields much larger signal-to-noise ratios for horizontal and vertical eye movement recordings compared to torsion. Figure 5.3 indicates the normal calculated level of system noise in relation to tOKN responses from all subjects across both stimulus velocities.

5.4.2. Influence of the pursuit system

The torsional OKN response is essentially involuntary and not influenced by voluntary pursuit mechanisms. Normally we have limited capacity to make voluntary torsional eye movements in the primary position, although one early previous report by Balliet & Nakayama (1978) have suggested that, with training, torsional pursuit can be generated voluntarily. The torsional "pursuit" described, however, does not involve the classic pursuit mechanism of tracking a single object of interest but rather is driven by the alignment of an after image to static stimuli spanning the visual field. It is possible that tOKN is more prone to deterioration with age compared to horizontal and vertical OKN since pursuit cannot contribute to its generation.

The pursuit mechanism has been shown to decrease with age along the horizontal and vertical meridians (Simons & Buttner, 1985; Huaman & Sharpe, 1992; Demer, 1994). However, recent findings from a longitudinal study in normal older people (aged over 75 years) describes horizontal smooth pursuit gains at two different velocities not being greatly affected by aging (Kerber *et al.*, 2006). In comparison, horizontal OKN measures showed a gradual significant age-related decline over a 9 yr follow up period. It is possible that the rate of horizontal and vertical OKN decline could be slowed by contribution of the

pursuit system in contrast to the torsional OKN response which shows a much sharper decline.

5.4.3. Cortical link

The importance of higher cortical pathways compared to subcortical (retino-geniculate) pathways used for motion detection have been investigated with respect to the aging process (Tran *et al.*, 1998). Subjective measures of motion perception and objective measures of horizontal motion detection when viewing a random dot display were investigated in volunteers aged between 19-92 years of age. Interestingly, the authors found an age-related linear decrease in objective OKN responses as well as a subjective increase in the motion perception thresholds; however, they did not find an association between the two factors. This suggests that aging affects the neural mechanisms behind motion perception and motion detection at different cortical and subcortical levels.

5.4.4. Aging of vestibular eye movements

The effects of aging on torsional eye movements generated through vestibular stimulation have also been described. Torsional eye movements were measured using videooculography during stimulation of the vestibular nerve using galvanic vestibular stimulation (GVS) in 57 healthy subjects aged 20-69 years by Jahn *et al.* (2003). They found that the magnitude of induced static ocular torsion and torsional nystagmus increased from the fourth to the sixth decade but decreased in the seventh decade. Listing's plane, the axis of rotation that governs the torsional position of the eye at all gaze positions (Leigh & Zee, 2006), has also been examined with respect to age. It was found that

torsional position was more variable in older subjects (i.e. Listing's plane was thicker) compared to younger subjects when the whole body was repositioned to different static roll and pitch positions (Furman & Schor, 2003).

5.4.5. Loss of vergence / cyclovergence in older subjects

A further factor that could affect the absent tOKN in the older subjects could be related to the possibility of diminished vergence responses. Although all normal volunteers demonstrated normal binocular functions on an orthoptic examination, a subclinical impairment in vergence latency could have been present in the older volunteers. Rambold *et al.* (2006) reported in response to change in target disparity, older subjects (aged 56 years and above, n=11) demonstrated increased latency with decreased peak velocity and acceleration in vergence eye movements compared to younger subjects (aged details 32 years or younger, n=12). Although this shows horizontal vergence impairment, the cyclovergence response is a similar, smaller magnitude response. It is therefore possible that this also could be affected which in turn could affect the volunteer's ability to deal with stimuli moving in the torsional meridian.

There is no literature regarding cyclovergence responses and the effect of age in normal subjects. Impaired vergence responses and in turn torsional OKN responses as a result of not wearing a presbyopic correction was ruled out as volunteers sat 1.2 metres away from the stimulus. None of the normal volunteers reported any torsional or horizontal diplopia when viewing the stimulus so any moderate impairment of vergence was ruled out as a contributing factor.

6. Experiment 4: tOKN in Strabismus

6. Experiment 4: tOKN in Strabismus

6.1. Patient recruitment

Table 6.1 summarises the clinical characteristics of all patients that participated in this experiment. Sixteen patients with either essential infantile esotropia syndrome (EIES) (n=7) or childhood strabismus (CS) (n=9) (aged between 19 and 47 years, average = 35.1 years SD = 8.95 years). Patients less than 50 years of age were used in this experiment to rule out any possible aging effect on tOKN generation as was investigated in experiment 3. The childhood strabismus group comprised of primary (n=5), consecutive (n =3) (previous esotropia that had become exotropia after surgery) and residual strabismus (n=1) (previous esotropia remaining reduced esotropia after surgery). None of the subjects had binocular vision; one subject with EIES (*S1*) had demonstrated some potential for binocular vision in previous hospital notes. All patients were recruited from hospital ocular motility clinics at the Leicester Royal Infirmary, University Hospitals of Leicester NHS trust.

All patients that were selected for suitability in this experiment had their hospital records carefully inspected before being invited to participate. Full ophthalmological and orthoptic examination had been performed on all patients in their hospital records and their diagnosis was well established. If patients were recalled after a long period of being discharged they were examined for any new changes to their eyes. Any patients with any new ocular pathology from taking a history and examination were excluded from the study. Patients that had dissociated vertical deviation (DVD), latent nystagmus (LN) and manifest strabismus were classified as having EIES. The remaining subjects were recruited on the basis of the presence of long term strabismus and the presence of amblyopia both of which are markers of interruption to normal binocular vision development.

Patients were given and information sheet to read and informed written consent was given prior to taking part in the study.

6.2. Procedure

The optokinetic system was stimulated monocularly in all three directions of rotation to establish any asymmetries in the horizontal, vertical and torsional directions in both dominant and non-dominant eyes of all patients.

Horizontal and vertical OKN was recorded using an EyeLink pupil tracker (SMI GmbH, Berlin, Germany) at 250Hz while viewing stimuli projected on a rear projection screen (1.75m x1.17m) using a video projector (Hitachi CP-X958). This system was used when recording hOKN and vOKN because of higher resolution of recording in horizontal and vertical meridian compared to the *Strabs* system. Although each eye was calibrated prior to recording individually within the *EyeLink* set-up, offline calibration of data was also performed as this allowed for greater accuracy. This calibration was done by selecting data points when the patient was steadily fixating points horizontally and vertically at ±15° eccentricity and 0°. The hOKN stimuli consisted of a vertical square wave modulated contrast grating subtending 0.23 cycles/degree (whole field of 16 alternating black and white stripes), with one 1 cycle subtending 4.4º) (See *movie B* in *additional addenda CD*). The vOKN stimuli consisted of the same grating pattern in the horizontal orientation also subtending 0.23 cycles /degree (whole field is 12 alternating black and white stripes (1 cycle 4.4°). Both stimuli moved at a constant velocity at 10°/s, 20°/s and 40°/s. A nine-point calibration test was performed monocularly with each eye fixing eye individually. The non fixing eye was covered using a black cardboard occluder.

					Visual Acuity		
ID	**Age**	**Sex**	**Dom. Eye**	**Diagnosis**	**Right**	**Left**	**Orthoptic Status**
S1	20	M	RE	EIES	6/5	6/5	Decompensating esophoria / LE esotropia, LN, DVD
S2	24	F	LE	EIES	6/12+2	6/9	Residual RE hypertropia, LN, DVD
S3	33	M	RE	EIES	6/9	6/12	LE esotropia, LN, DVD
S4	40	M	LE	EIES	6/9	6/6	Secondary alternating exotropia, LN, DVD
S5	33	F	RE	EIES	6/6	6/6	LE hypertropia, LN, DVD
S6	19	M	RE	EIES	6/5	6/6ph	Residual LE esotropia, RE hypertropia, LN, DVD
S7	35	M	RE	EIES	6/6	6/6	LE esotropia, LN, DVD
S8	31	M	LE	Consec. Exo.	6/24	6/5	RE exotropia, RE hypertropia
S9	37	M	LE	Consec. Exo.	6/9	6/5	RE exotropia, RE hypertropia
S10	35	F	LE	Residual Eso.	6/24	6/4	RE esotropia
S11	41	F	LE	Primary Exo.	6/5	6/18	LE exotropia
S12	46	F	LE	Primary Eso.	6/9	6/5	RE esotropia
S13	46	F	RE	Primary Alt. Eso.	6/6	6/6	Alternating esotropia
S14	47	F	RE	Consec. Exo.	6/5	6/24	LE exotropia, LE hypertropia
S15	30	F	RE	Primary Alt. Eso.	6/5	6/6	Alternating esotropia
S16	45	F	LE	Primary Accom. Eso.	6/6	6/24	LE esotropia

Table 6.1. *Clinical characteristics of all strabismus patients used in experiment 4. (Age(yrs), Dom eye = dominant eye, Visual acuity (Snellen), EIES = essential infantile esotropia syndrome, Consec = consecutive, Alt = alternating, Accomm= accommodative, RE = right eye, LE = left eye, LN= latent nystagmus, DVD = dissociated vertical deviation).*

The tOKN stimulus used and torsional eye movement recording was done as described above in sections 2.2 and 5.1. The stimulus velocities used to elicit tOKN in the patients was 40°/s, 200°/s and 400°/s in both clockwise and anticlockwise directions. A stimulus velocity of 200°/s was used in addition in all patients to see if a response was evident at this velocity when not present at 400°/s.

As monocular recordings were taken, the direction of the eye rotation and the velocity of the stimulus were defined in relation to the viewing monocular eye. For tOKN this is described in section 5.1. For hOKN, with the right eye open if the stimulus was moving to the right of the patient, this would result in a slow phase in the temporalward direction relative to the RE viewing. If the stimulus was moving to the left this would result in a slow phase in the nasalward direction relative to right eye.

A control group of 15 healthy subjects (6 male, 9 female) aged between 19 to 56 years (mean age: 36 S.D: 11.9) was used to compare to the patient group. The entire control group had visual acuity of 6/9 or better in each eye and an orthoptic examination excluded any ocular motility and binocular vision defects.

6.3. Data analysis

The digitised ASCII file output for horizontal vertical data from the EyeLink recordings were converted into Spike 2 software files (Cambridge Electronic Design, UK) for analysis. A velocity threshold was used to determine saccades in the recordings. The slow phase velocity was calculated from the mean value in the velocity channel during each slow phase to give the (MSPV).

Linear mixed models were used to statistically compare the effects of stimulus direction in the normal subjects and strabismic patients with stimulus velocity and direction used as fixed factors.

The asymmetry index (AI) was calculated using the following formula:

Horizontal AI = nasalward gain / (nasalward gain+ temporalward gain)

Vertical AI = upward gain / (upward gain+ downward gain).

A comparison of asymmetries found in the horizontal and vertical directions between both groups, was also performed using the same statistical technique including subject group and stimulus velocity as fixed factors. A comparison of torsional optokinetic response in normals and stabismics was made using Pearson's Chi-square test.

6.4. Results

6.4.1. Original Data

Figure 6.1 shows original recordings of monocular horizontal, vertical (stimulus velocity 10°/s) and torsional optokinetic nystagmus (stimulus velocity 40°/s) in one representative normal subject.

The hOKN response is symmetrical in both nasalward and temporalward directions (6.1(a)). The vertical OKN response demonstrates a greater amplitude of response to upward moving stimulation compared to downward stimulation (6.1(b)) and the tOKN response is symmetrical in both intorsion and extorsion directions (6.1(c)).

Figure 6.2 shows original OKN recordings from a representative strabismic patient (EIES) in the horizontal, vertical (stimulus velocity 10°/s) and torsional (stimulus velocity 40°/s) directions in the dominant and non-dominant eyes. Figure 6.2 (a) shows the patient to have a greater response in the nasalwards direction compare to temporalward direction in the dominant and non-dominant eye. A very slightly better response to upward moving stimuli compared to downward moving stimuli in the dominant and non dominant eye is shown in Figure 6.2 (b). No response for torsional OKN stimulation in the non dominant eye in either direction of rotation is shown in figure 6.2 (c) and a small response in the intorsion direction with the dominant eye. In total, recordings from 16 patients with EIES were analysed and compared to age-matched normal subjects. The results of the analysis of all recordings are shown in scatter plots on Figures 6.4, 6.5 and 6.6.

6.4.2. Correlation of gains for normal subjects along each axis

6.4.2.1. Horizontal OKN

Figure 6.3 (a) shows scatter plots of horizontal OKN gain for the three stimulus velocities of 10, 20 and 40°/s stimulation for all normal subjects in the dominant and non-dominant eyes. All points for normal subjects lie close or on the line of unity showing no asymmetry of response. The average gain for temporalward stimulation was 0.73 and 0.72 for non-dominant and dominant eyes, respectively. The average gain for nasalward stimulation was 0.74 and 0.69 for non-dominant and dominant eyes, respectively. There was no significant directional differences for both eyes *(p*>0.05).

Figure 6.1. *Original monocular optokinetic nystagmus recordings from one normal subject in the horizontal, vertical and torsional directions.*

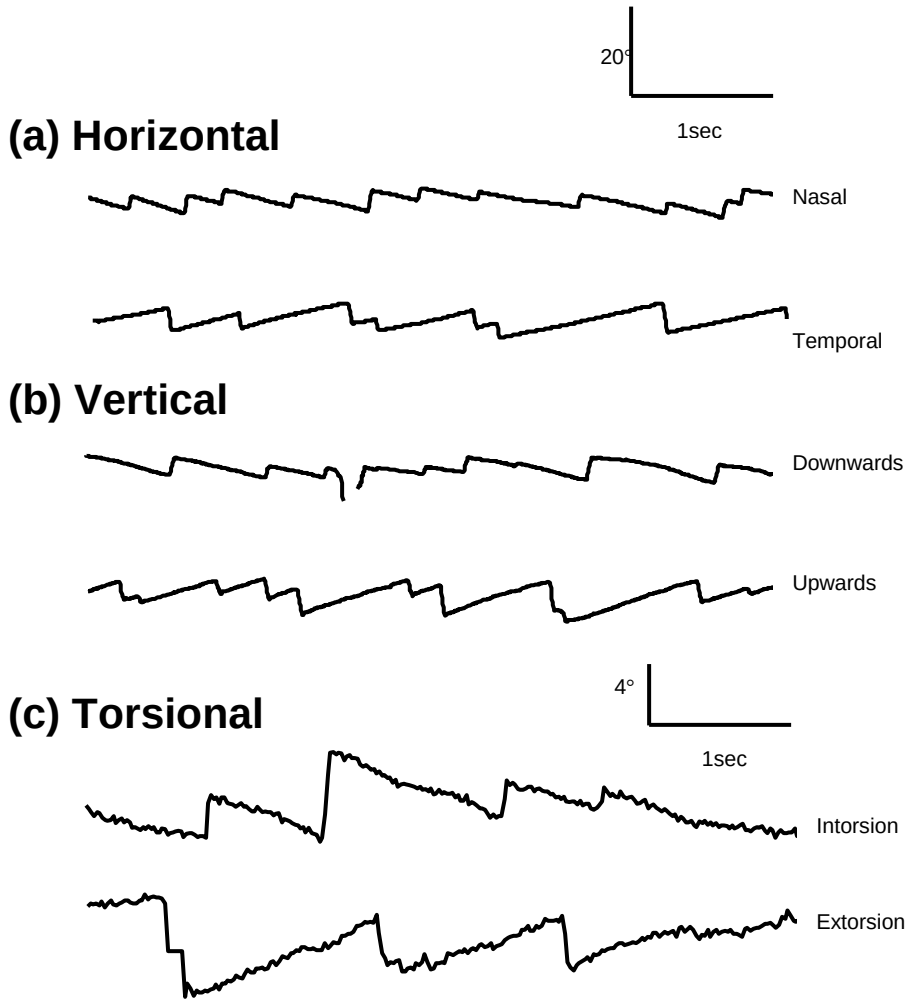
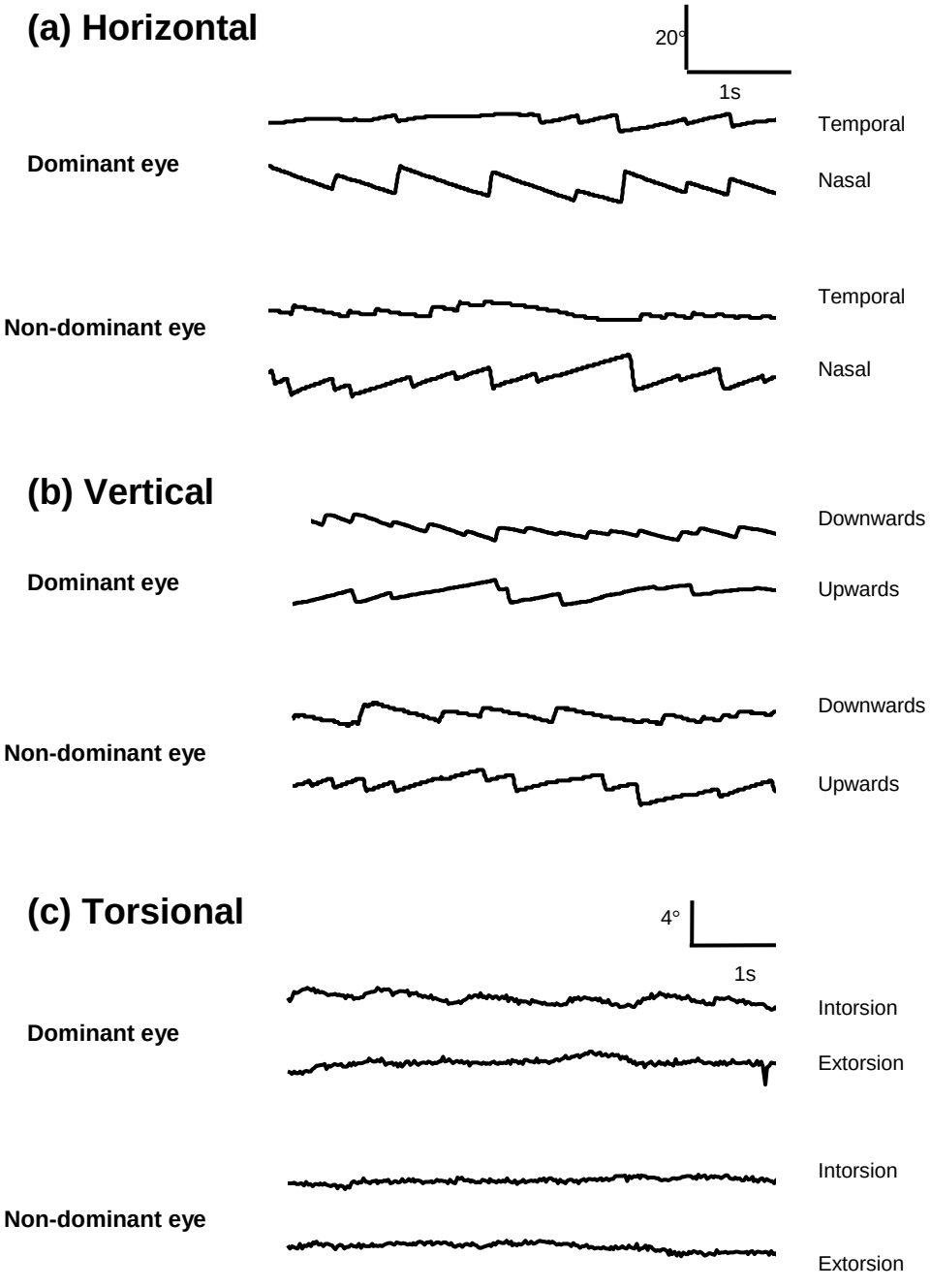


Figure 6.2. *Original monocular OKN recordings from one strabismus patient in the dominant and non-dominant eyes in the (a) horizontal, (b) vertical and (c) torsional directions.*



6.4.2.2. Vertical OKN

Figure 6.4 (a) shows scatter plots of gain for vertical OKN stimulation across the three stimulus velocities of 10, 20 and 40°/s in all normal subjects. Most of the points for normal subjects lie below line of unity showing an asymmetry of response with upward gain greater than downward gain. The average gain for downward moving stimuli was 0.47 and 0.45 in non-dominant and dominant eyes, respectively. For upward stimulation the average gain was 0.64 and 0.62 in non-dominant and dominant eyes, respectively, indicating an up-down asymmetry which was highly significant (F =41.02 p=1.49x10^{-8} for the non dominant eye, F=37.12 p=5.59x10^{-8} for the dominant eye).

6.4.2.3. Torsional OKN

Figure 6.3 (a) shows a scatter plot of tOKN MSPV in both intorsion and extorsion directions of all the normal subjects in the dominant eye. MSPV was used to plot the data as gain values across stimulus velocities were too far apart to assess asymmetry on the same scale. All points for normal subjects lie close or on the line of unity showing no asymmetry of response for extorsion and intorsion directions. The average MSPV was 1.82°/s and 1.68°/s for extorsion and intorsion directions respectively. There was no significant directional preponderance demonstrated (F=0.50, p=0.48).

Figure 6.3. *Scatter plots of* ***horizontal*** *OKN gain across all stimulus velocities in (a) normal subjects and (b) strabismics. Points falling above the unity line indicate temporalward gain being greater than nasalward gain. Points falling below the line indicate nasalward gain greater than temporalward gain.*

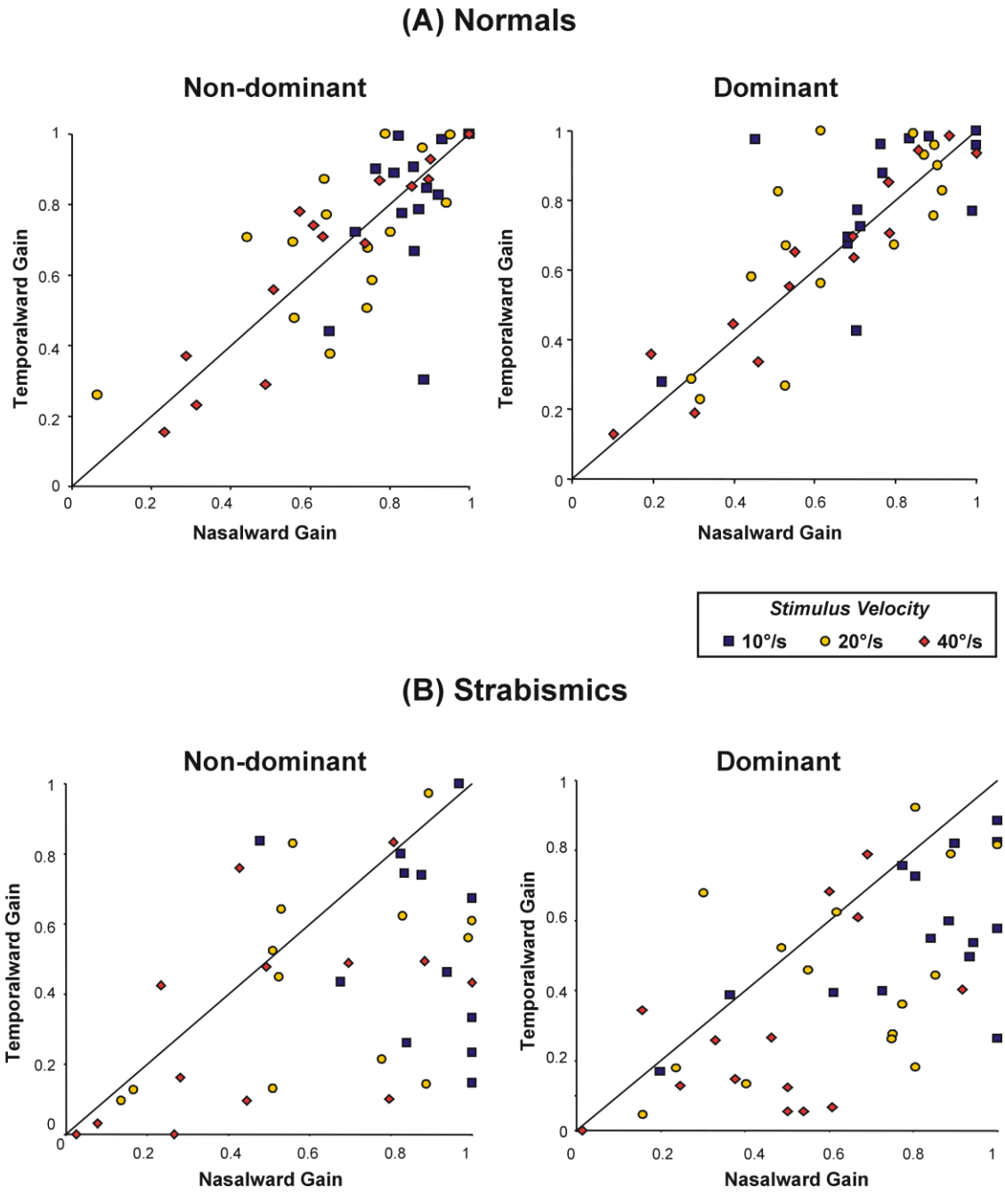


Figure 6.4. *Scatter plots of* ***vertical*** *OKN gain across all stimulus velocities in (a) normal subjects and (b) strabismics. Points falling above the unity line indicate downward gain being greater than upward gain. Points falling below the line indicate upward gain greater than downward gain.*

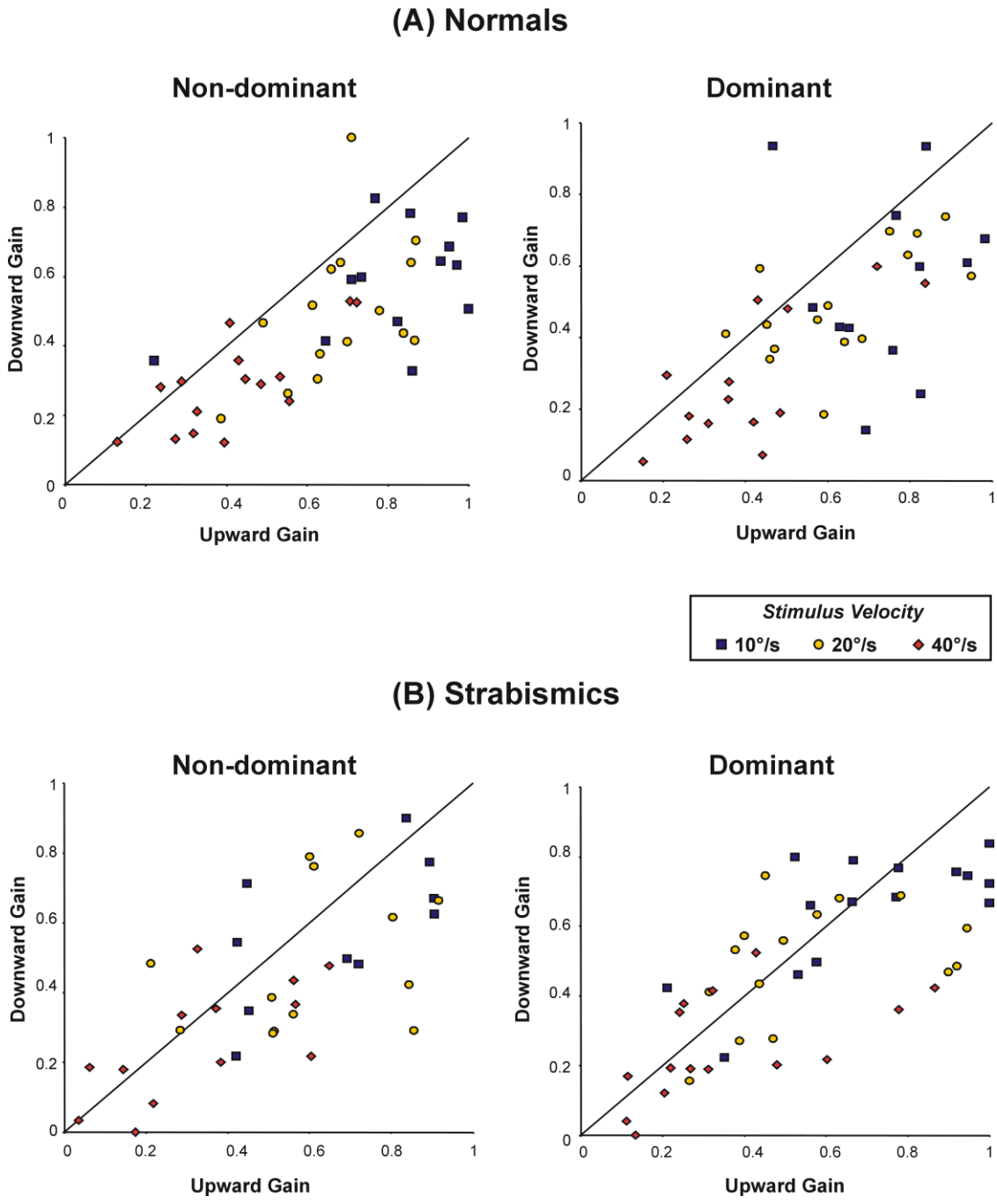
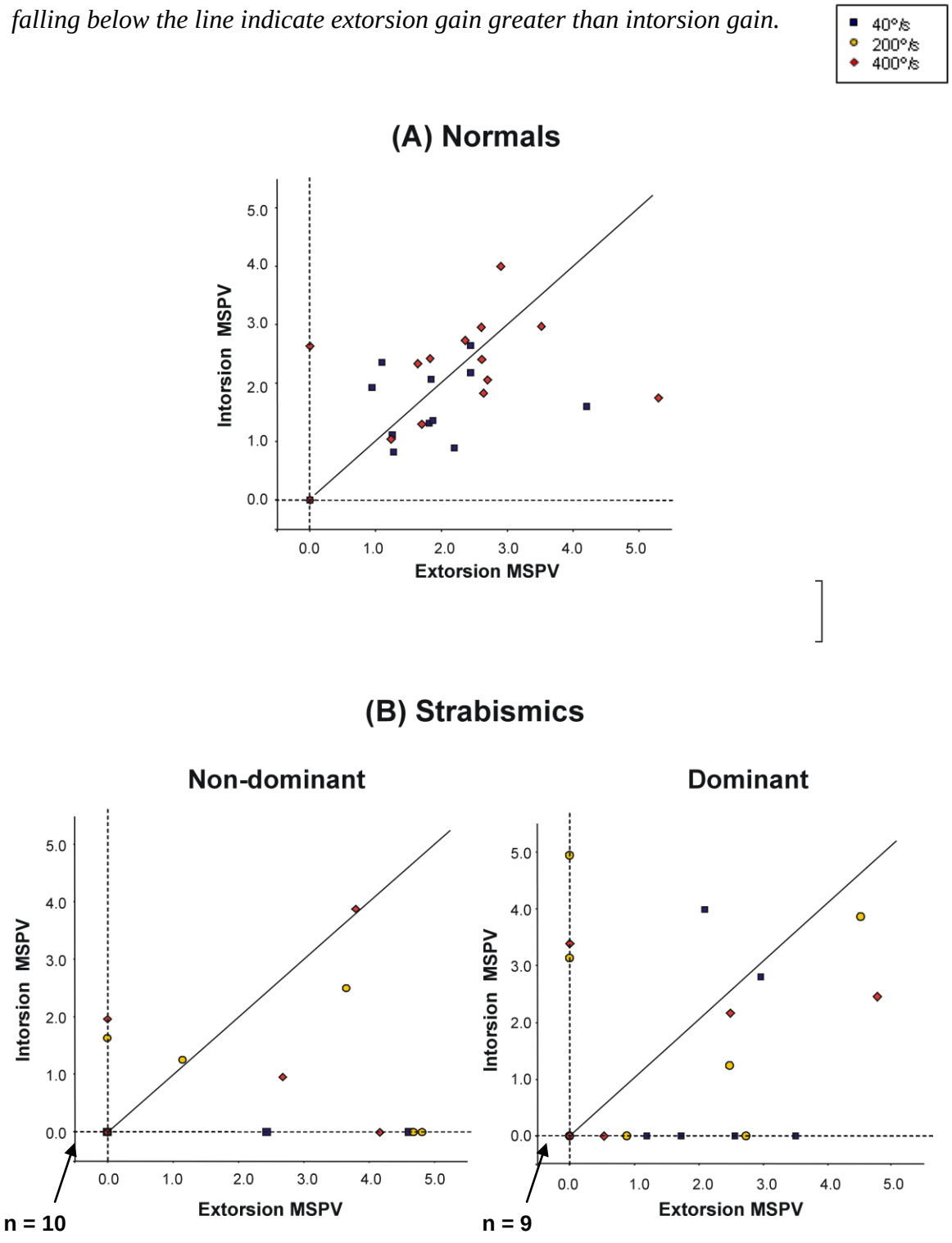


Figure 6.5. *Scatter plots of* ***torsional*** *OKN gain at 40°/s and 400°/s stimulation in (a) normal subjects and at 40°/s, 200°/s and 400°/s in (b) strabismics. Points falling above the unity line indicate intorsion gain being greater than extorsion gain. Points falling below the line indicate extorsion gain greater than intorsion gain.*



6.4.3. Correlation of gains for strabismus patients along each axis

6.4.3.1. Horizontal OKN

Figure 6.3 (b) shows scatter plots for gain in the strabismic subjects for all three stimulus velocities for horizontal OKN stimulation. Most points fall below the line of unity showing nasalward gain being greater than temporalward gain. The average gain for temporalward motion across all stimulus velocities was 0.45 and 0.43 for non-dominant and dominant eyes, respectively. The average gain for nasalward stimulation across all stimulus velocities was 0.68 and 0.65 for non-dominant and dominant eyes, respectively. This indicated a temporal to nasal asymmetry (temporal gain greater than nasal) which was highly significant (F=26.02, p=3.64 x10^{-6} for the non-dominant eyes, F=43.68, p=7.18 x 10^{-9} for the dominant eyes).

6.4.3.2. Vertical OKN

Figure 6.4 (b) shows scatter plots for vertical OKN stimulation at all three stimulus velocities in strabismics. Although most points fall below unity line, showing upward gain to be greater than downward, there are also some points above the unity line showing the converse effect. The average gain for vOKN stimulation across all stimulus velocities for the strabismic group was 0.47 and 0.46 for downward moving stimuli in the non-dominant and dominant eyes, respectively, and 0.56 and 0.54 for upward moving stimuli in non-dominant and dominant eyes. This indicated a small reduction in the upward direction in comparison to the normal subject group. However, there was still a significant up–down asymmetry (up greater than down) (F=9.62, p=0.0029 for non-dominant eye, F=8.72, p=0.0043 for the dominant eyes).

6.4.3.3. Torsional OKN

Linear mixed model analysis of the data could not be performed for torsional OKN in strabismics because the majority this group did not show tOKN as indicated by zero MSPV on the scatter plot (see section 6.4.2.3.).

6.4.4. Comparison of mean gains in strabismic and control subjects for hOKN and vOKN

Figures 6.6 and 6.7 compare mean gain (± SEM) for strabismic and controls at 10, 20, and 40°/s in non-dominant and dominant eyes in the horizontal and vertical OKN directions, respectively.

6.4.4.1. Horizontal OKN

Temporalward gain was significantly reduced in the strabismic patients when compared to normal subjects in both non-dominant and dominant eyes (F=22.92, p=7.86x10^{-6} for the non-dominant eye, F=25.88, p=2.26x10^{-6} for the dominant eye). There was no significant difference in nasalward gain in either eye between each group (F=1.07, p=0.31 for the non-dominant eye, F=0.65, p=0.42 for the dominant eye (see Figures 3.17(i) and 3.18(i)). For the normal subjects, the mean (± SEM) hOKN gain was highest at 10°/s stimulation in temporalward (0.8±0.06 (dominant eye), 0.81±0.06 (non dominant eye)) and nasalward (0.75±0.06 (dominant eye), 0.85±0.02 (non- dominant eye) directions.

For the strabismic patients, the mean gain was also highest at 10°/s stimulation in temporalward (0.56±0.06 (dominant eye), 0.57±0.08 (non-dominant eyes)) and nasalward directions (0.82±0.07 (dominant eyes), 0.9±0.05 (non-dominant eyes)).

6.4.4.2. Vertical OKN

Upward gain was very slightly reduced in the strabismic patients when compared to normal subjects but was not statistically significant (F=3.13, p=0.08 for the non-dominant eye, F=1.50, p=0.23 for the dominant eye). There was no difference in downward vOKN gain between both groups (F= 0.0018, p=0.97 for the non-dominant eye, F=0.16, p=0.70 for the dominant eye).

For the normal subjects, the mean (±SEM) vOKN gain was highest at 10°/s stimulation in upward (0.81±0.05 (dominant eye), 0.83±0.05 (non-dominant eye)) and downward (0.58±0.06 (dominant eye), 0.61±0.04 (non- dominant eye)) directions.

For the strabismic patients, the mean gain was also highest at 10°/s stimulation in upward (0.73±0.07 (dominant eye), 0.75±0.06 (non-dominant eyes)) and downward (0.65±0.04 (dominant eyes), 0.65±0.07 (non-dominant eyes)) directions.

Figure 6.6. *Mean(± SEM) OKN gain in the (i) horizontal and (ii) vertical directions in the strabismic and normal subjects for all three stimulus velocities in the* ***non-dominant*** *eye. Temporalward gain was significantly reduced in the strabismic patients (see i). Upward gain was very slightly reduced in the strabismic patients but was not significant (see ii).*

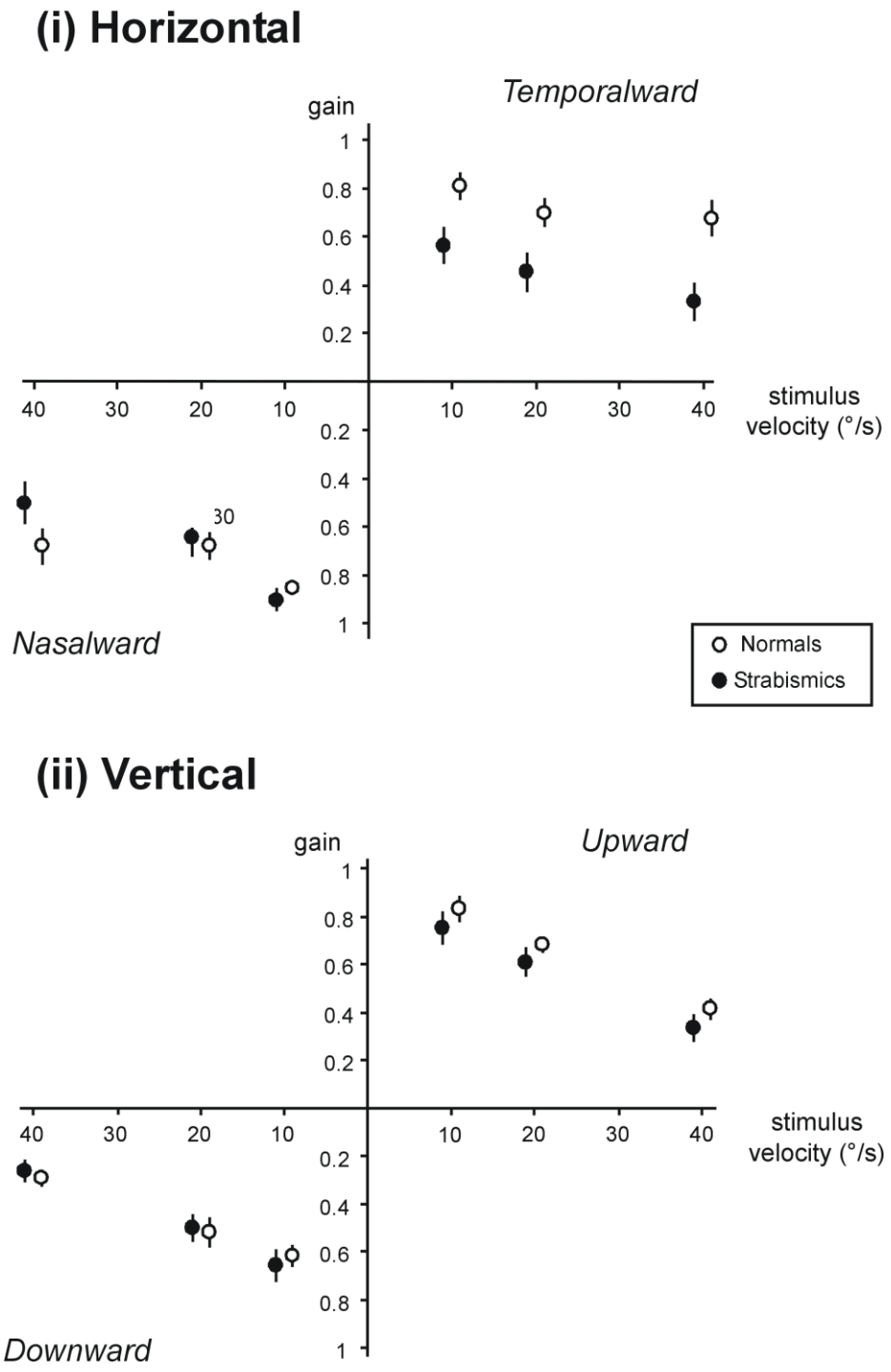
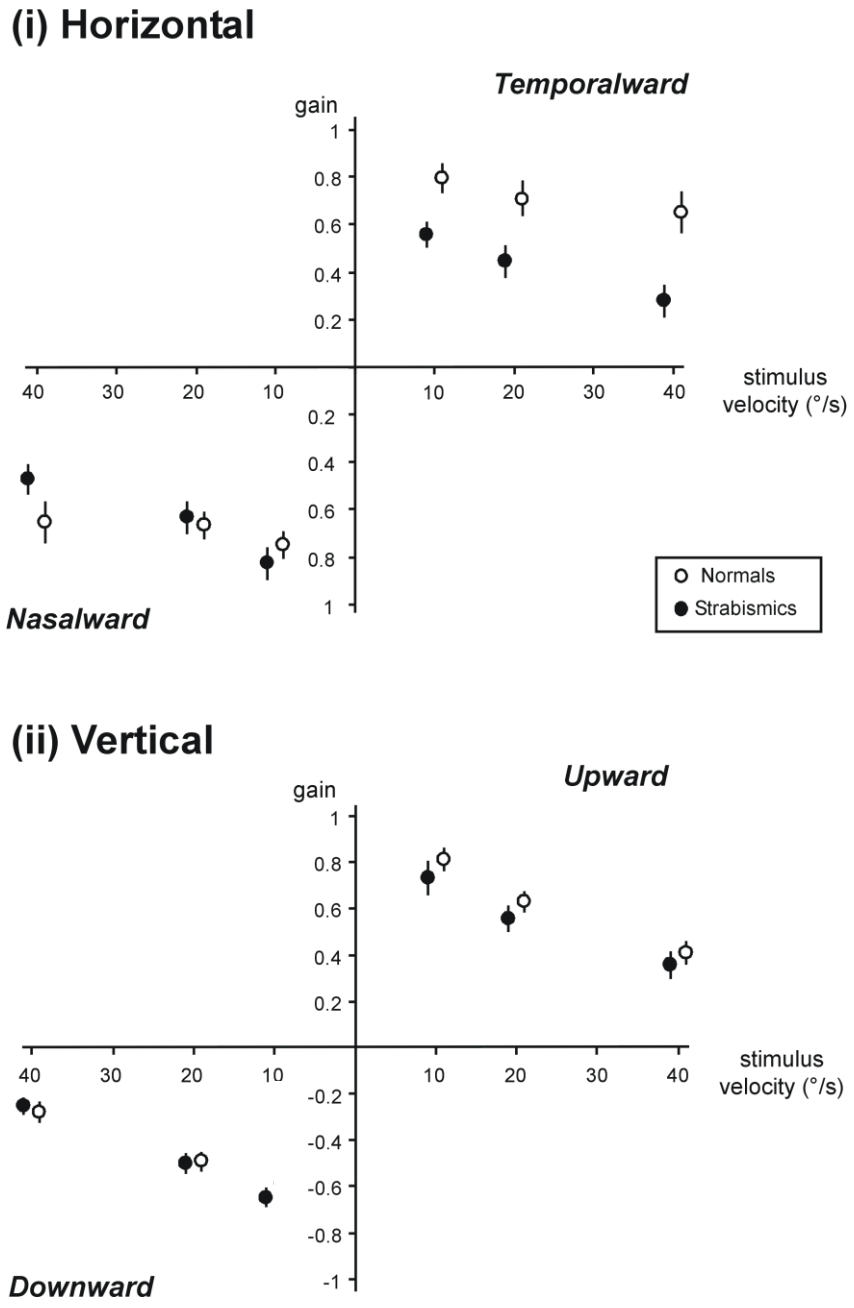


Figure 6.7. *Mean (± SEM) OKN gain in the (i) horizontal and (ii) vertical directions in the strabismic and normals subjects for all three stimulus velocities in the* ***dominant*** *eye. Temporalward gain was significantly reduced in the strabismic patients (i). Upward gain was very slightly reduced in the strabismic patients but was not significant (ii).*



6.4.5. Comparison of asymmetry indices in strabismic and normal subjects for hOKN and vOKN

The asymmetry of hOKN and vOKN in the strabismic patients (EIES and CS) were compared to age-matched normal subjects. There was a significant difference in hOKN asymmetry index found between both groups (strabismics and normals) when comparing non-dominant and dominant eyes (F=10.19, p=0.0037 in the non-dominant eye and F=16.13, p=0.0040 for the dominant eye). There was no significant difference when comparing asymmetries in vOKN in both groups (p>0.05).

Table 6.2 *Significance levels for comparison of horizontal and vertical OKN asymmetry between the strabismus patient group and the normal subject group in the dominant (DOM) and non-dominant (NDOM) eyes using linear mixed models (significant values highlighted in blue).*

		Significance	
Eye	**OKN direction**	***F***	***p***
NDOM	Horizontal(AI)	10.19	0.0037
DOM	Horizontal(AI)	16.13	0.0004
NDOM	Vertical(AI)	0.76	0.39
DOM	Vertical(AI)	0.79	0.38

6.4.6. Torsional OKN (Responders versus Non-responders)

Figure 6.5 (b) shows scatter plots of MSPV across both stimulus velocities in both intorsion and extorsion directions for non-dominant and dominant eyes of the strabismic subjects. There was no specific asymmetry of response in either direction, although numbers of tOKN responses were much lower than for hOKN and vOKN.

Tables 6.3 and table 6.4 shows the tOKN data from all subjects in the dominant and non-dominant eyes. Of the 16 patients tested 8 subjects did not respond to any tOKN stimulation at either stimulus velocity or direction with their non-dominant eye and 4 subjects showed no response in their dominant eye. Two subjects showed no response in one rotation direction with their non-dominant eye. Six subjects showed no response in one rotation direction in their dominant eyes.

Patients S4, S6 and S8 demonstrated "V" patterns in their strabismus and patient S11 showed an "A" pattern strabismus, this did not correlate with the presence or absence of tOKN in these patients.

The proportions of responders and none responders were compared between strabismic subjects and age matched controls using Pearson's Chi-square test. There was a significant difference in proportions of responders and non-responders for three of the four experimental conditions (intorsion at 40°/s, extorsion and intorsion at 400°/s indicated in blue) for the dominant eye (Table 6.5).

Table 6.5 *Significance values (p) and Pearson Chi-square values (with Yates' continuity correction) comparing responders and non-responders in strabismics and normal subjects.*

Direction	Velocity (°/s)	*p*	Pearson Chi-Square
Extorsion	40	0.14	2.16
Intorsion	40	0.0024	9.19
Extorsion	400	0.040	4.24
Intorsion	400	0.0085	6.93

Dominant

			Extorsion (SPV)			Intorsion (SPV)			Vertical (gain)		Horiz. (gain)	
ID	**Dom. Eye**	**Diagnosis**	40°/s	200°/s	400°/s	40°/s	200°/s	400°/s	U	D	N	T
S1	RE	EIES	×	×	×	×	×	×	0.35	0.45	0.71	0.31
S2	LE	EIES	2.97	2.49	2.50	2.79	1.24	2.16	0.86	0.62	0.60	0.44
S3	RE	EIES	×	2.74	×	×	×	×	0.85	0.51	0.72	0.36
S4	LE	EIES	2.57	×	×	×	-	×	0.24	0.25	0.56	0.20
S5	RE	EIES	×	×	×	×	3.13	3.39	0.44	0.32	0.79	0.19
S6	RE	EIES	-	-	1.76	-	-	-	0.41	0.63	0.90	0.46
S7	RE	EIES	1.20	0.89	-	×	×	×	0.46	0.48	0.76	0.27
S8	LE	Consec. Exo.	×	×	×	×	×	×	0.48	0.44	0.28	0.23
S9	LE	Consec. Exo.	2.10	×	-	3.99	4.93	4.64	0.53	0.58	0.80	0.84
S10	LE	Residual Eso.	3.51	4.52	4.78	×	3.86	2.45	0.99	0.56	0.66	0.69
S11	LE	Primary Exo.	1.74	×	×	×	×	×	0.25	0.13	0.12	0.07
S13	RE	Primary Alt. Eso.	-	-	-	×	×	×	0.59	0.59	0.91	0.74
S14	RE	Consec. Exo.	×	×	×	×	×	-	0.58	0.66	1.00	0.85
S15	RE	Primary Alt. Eso.	×	×	×	×	×	×	0.35	0.33	0.36	0.47
S16	LE	Primary Accom. Eso.	×	×	0.53	×	×	×	0.87	0.45	0.56	0.48

Table 6.3 *Mean tOKN slow phase velocities (SPV) of all strabismus patients in the dominant eye. Responses to all three stimulus velocities in extorsion and intorsion directions is shown (×=no tOKN response,(-)= poor recording. The dominant eye recording from Patient S12 was excluded from analysis as the recording was too poor. Average vOKN (U= upwards D=downwards) and hOKN (N= nasalward, T= temporalward) gain in the same patients is also shown for comparison.*

Non Dominant

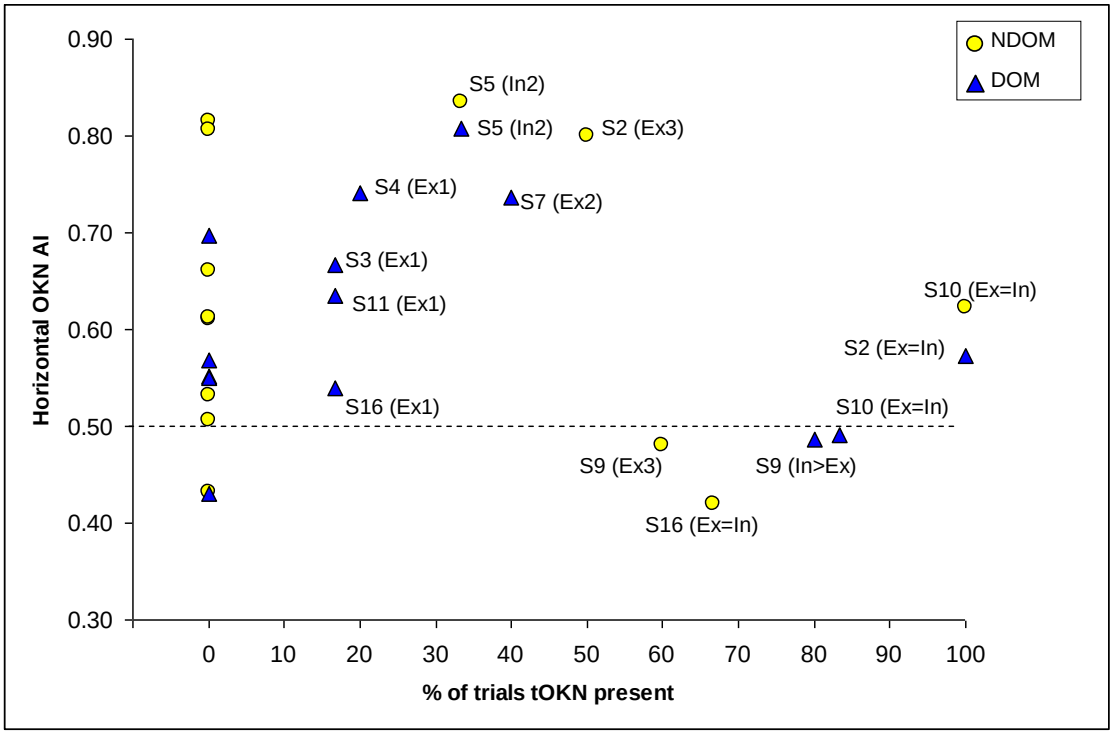
			Extorsion (SPV)			Intorsion (SPV)			Vertical (gain)		Horiz. (gain)	
ID	**Dom. Eye**	**Diagnosis**	40°/s	200°/s	400°/s	40°/s	200°/s	400°/s	U	D	N	T
S1	RE	EIES	×	×	×	×	×	×	0.24	0.46	0.54	0.48
S2	LE	EIES	2.44	4.81	4.16	×	×	×	0.77	0.67	0.86	0.22
S4	LE	EIES	×	×	×	×	-	×	0.34	0.20	0.45	0.10
S5	RE	EIES	×	×	×	×	1.64	1.97	0.39	0.24	0.79	0.16
S6	RE	EIES	×	×	×	×	×	×	0.62	0.64	1.00	0.53
S7	RE	EIES	×	×	×	×	-	×	0.64	0.33	0.82	0.52
S9	LE	Consec. Exo.	4.61	4.68	8.09	×	×	-	0.68	0.75	0.89	0.96
S10	LE	Residual Eso.	3.17	3.65	3.79	-	2.51	3.89	0.79	0.57	0.98	0.59
S12	LE	Primary Eso.	×	×	×	×	×	×	0.39	0.26	0.28	0.18
S13	RE	Primary Alt. Eso.	×	×	×	×	×	×	0.57	0.46	0.63	0.62
S14	RE	Consec. Exo.	×	×	×	×	×	×	0.72	0.78	0.60	0.80
S15	RE	Primary Alt. Eso.	×	×	×	×	×	×	0.36	0.34	0.54	0.13
S16	LE	Primary Accom. Eso.	×	1.15	2.67	×	1.26	0.96	0.86	0.43	0.41	0.57

Table 6.4 *Mean tOKN slow phase velocities (SPV) of all strabismus patients in the non-dominant eye. Responses to all three stimulus velocities in extorsion and intorsion directions is shown (× =no tOKN response,(-)= poor recording. Patients S3, S8 and S11 were unable to fixate the tOKN stimulus well enough with their non-dominant eye to perform an accurate eye recording. Average vOKN (U= upwards D=downwards) and hOKN (N= nasalward, T= temporalward) gain in the same patients is also shown for comparison.*

6.4.7. Comparisons of tOKN, hOKN and vOKN

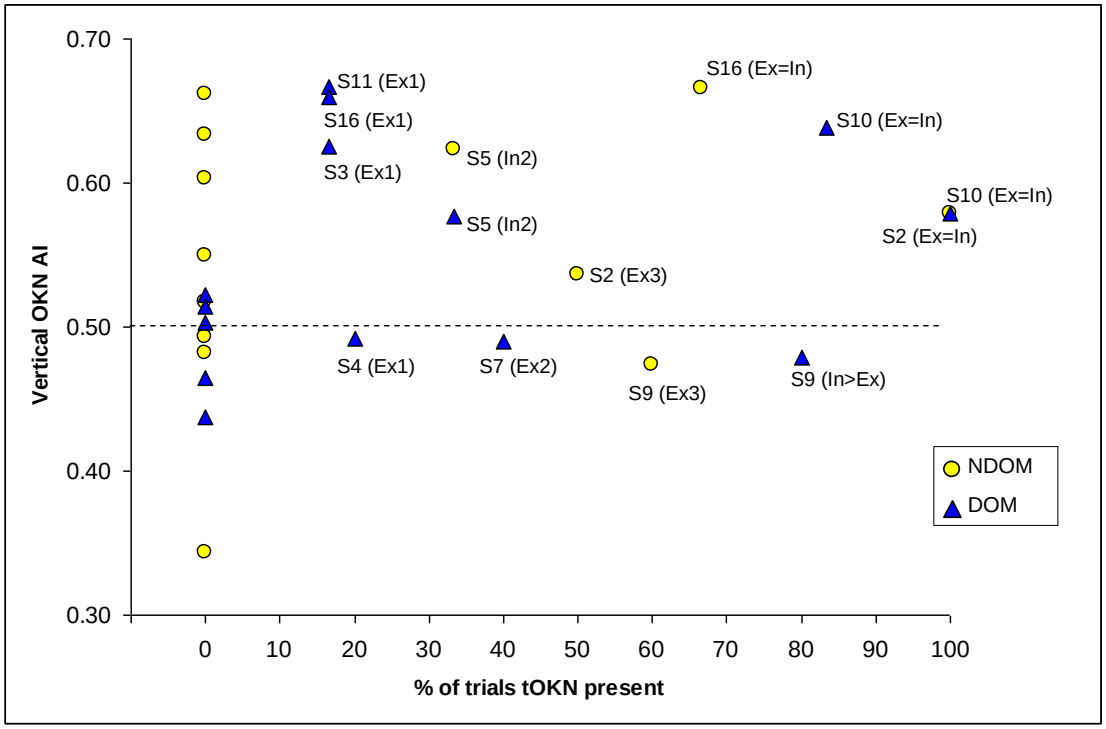
Figures 6.8 shows the presence and direction of tOKN (*extorsion = Ex, intorsion =In*) across all trials in the sixteen strabismic patients (*S1 to S16 on tables 6.3 and 6.4)* plotted against hOKN asymmetry indices (AI).

Figure 6.8. *Relationship between tOKN incidence (% across all trials) and hOKN AI for all strabismic patients in the non-dominant (NDOM) and dominant eyes (DOM). AI greater than 0.5 indicates nasalward gain greater than temporalward gain. The label adjacent to each point refers to the patient number, and in brackets, the direction tOKN present and number of trials present in that direction, eg. S7(Ex2) refers to patient S7 showing tOKN in extorsion direction only in two trials.(In=intorsion, Ex=extorsion, AI= asymmetry asymmetry index.)*



Figures 6.9 shows the presence and direction of tOKN (*extorsion=Ex, intorsion =In*) across all trials in the sixteen strabismic patients (*S1 to S16 on tables 3.3 and 3.4)* plotted against hOKN asymmetry indices (AI).

Figure 6.9. *Relationship between tOKN incidence (% across all trials) and* ***vOKN.*** *AI for all strabismic patients in the non-dominant (NDOM) and dominant eyes (DOM). AI greater than 0.5 indicates upward gain greater than downward gain. The label adjacent to each point refers to the patient number (direction and number of trials tOKN is present). In=intorsion, Ex=extorsion.*



Of the 10 patients that had a tOKN response, 5 had a response in the extorsion direction alone with their dominant eyes and 2 had a response in the extorsion direction

alone in the non-dominant eye. One patient responded in the intorsion direction alone with both eyes. Three patients had an equal response in intorsion and extorsion directions.

There did not appear to be any consistent correlation with the proportion or direction of responses to tOKN stimuli and the asymmetry of their hOKN and vOKN responses. A slight trend was noted when looking at responses of the dominant and non-dominant eyes in response to vertical OKN stimulation in the upward direction as the subjects with the highest vertical OKN gains for upward stimulation (i.e. asymmetry index greater than 0.5 on Figure 3.20) were also patients who displayed a torsional OKN response. This however was not significant ($p>0.05$, $F=2.18$ $p=0.14$).

6.5. Discussion

This study has compared for the first time the horizontal, vertical and torsional optokinetic responses in normal volunteers and patients with essential infantile esotropia syndrome (EIES) and childhood strabismus (CS). The horizontal and torsional OKN responses significantly deviated from normal responses across all patients. There was no significant difference in vertical OKN between normals and strabismic patients.

6.5.1. Normal subjects

The hOKN response in the normal subjects was symmetrical for both temporalward and nasalward stimulation agreeing with previous literature (Schor & Levi, 1980; Howard, 1997). The vOKN response displayed a significant asymmetry as upward vOKN gain was greater than downward OKN gain agreeing with previous literature (Bahill, 1975; Matsuo & Cohen, 1984; van den Berg & Collewijn, 1988; Murasugi & Howard, 1989b; Bohmer & Baloh, 1990; Ogino *et al.*, 1996; Garbutt *et al.*, 2003b). The

tOKN response in concordance with the hOKN response also displayed a symmetrical response for both intorsion and extorsion directions of rotation in agreement with previous literature (Cheung & Howard, 1991; Suzuki *et al.*, 2000).

6.5.2. Patients with EIES and CS

The hOKN monocular temporalward response was significantly reduced compared to normal values in strabismic patients in our study agreeing with previous studies (Schor & Levi, 1980; Westall & Shute, 1992; Aiello *et al.*, 1994; Wright, 1996a; Valmaggia *et al.*, 2003). This occurred in dominant and non-dominant eyes. Previous work has observed that this asymmetry occurs in both eyes if the strabismus occurred in early onset (Westall & Shute, 1992). This is also in agreement with the results of our study as all patients with EIES (i.e. early onset) showed a hOKN asymmetry in the dominant and non-dominant eyes.

When examining the vOKN response, strabismic patients in our study demonstrated no significant change in average gain compared to normal subjects for downward stimulation. However, they did demonstrate a small reduction from normal subjects in their upward OKN response (normals; 0.64, 0.62 in non-dominant and dominant eyes, respectively strabismics; 0.56, 0.54 for non-dominant and dominant eyes, respectively. Even with this small reduction in upwards response, there was still a significant preference for upwards stimulation in the strabismic patients. When comparing vOKN asymmetries (up versus down) of the strabismic patients to the normal subjects however, there was no significant difference found (p=0.39 for the non-dominant eyes and p=0.38 for the dominant eyes).

Previous authors have also commented on the reduction in downwards OKN in strabismics (Tychsen *et al.*, 1984; Garbutt *et al.*, 2003b). However, we observed little difference between strabismics and control subjects for downward vOKN. There is also no mention in previous literature of upward stimulation being the only direction affected in strabismus. Garbutt *et al.* (2003b) reported reduced velocities in both upwards and downwards stimulation in a small, varied sample of six patients with strabismus compared to normals. Schor & Levi (1980) reported a 10% reduction of slow phase velocity for upwards compared to downwards stimulation in 2/5 of the normal subjects used, however no comparison of gains was made to the twenty subjects with strabismic and anisometropic amblyopia when viewing vertical OKN stimuli. They also used a small number of control subjects to compare to their patient sample.

6.5.3. Torsional OKN and strabismus patients.

The most striking results were observed when we examined tOKN in the strabismic group. It was of interest to see a large number of subjects with no response to tOKN stimulation in any direction of rotation with variability in response between dominant and non-dominant eyes (i.e. non-responders - 8 of the 16 subjects when viewing the stimulus with the non-dominant eye, 4 subjects with the dominant eye). These same patients showed consistent hOKN and vOKN asymmetries (Tables 6.4 and 6.5). Of the subjects that did respond, there appeared to be a reduction in MSPV in comparison to normals in all directions except when the non-dominant eye rotated in the extorsion direction (MSPV 3.32º/s).

There did not appear to be any consistent pattern in those subjects that were non-responders to level of amblyopia or type of strabismus. For the dominant eyes, in patients who were non-responders, 1 patient had EIES and the remaining 3/4 had CS. For the non-dominant eyes, 4/8 non-responding patients had EIES and the remaining 4 had CS.

Although no previous work has been done on the tOKN response and the effect of ocular misalignment from birth or childhood, Washio *et al*. (2005) examined the tOKN response when binocular disparities were induced using alteration of viewing distance of a target and using prisms. This method in some ways simulates strabismus in normal subjects in that a retinal disparity is induced. However, healthy volunteers do not show the developmental neural changes associated with long term retinal disparity caused by strabismus. They found a significant increase in tOKN gain in all zero disparity conditions compared to when a crossed disparity was induced forcing the eyes to converge. Their results agree with previous work on horizontal OKN that shows a reduction in gain when a disparity was induced when viewing the visual target (Howard & Simpson, 1989). Patients in our study were either born with a manifest deviation or developed an eye deviation during childhood causing an interruption in their binocular vision development. This initial disparate input to their visual systems may well explain the complete absence of tOKN in some of our subjects. It is possible that some component of their tOKN system was unable to develop normally, such as the cortical motion centres that have been shown to be affected in aging described earlier (Tran *et al.*, 1998).

6.5.3.1. Influence of vergence eye movements

Normally, it is the vergence system that is used to maintain binocular alignment in all three meridians, and it has been demonstrated that normal infants are able make vergence movements at 3 months of age (Horwood, 2003). If however there is a disorder of this system, then strabismus results (Von Noorden, 1977). All patients from our study, in both groups, had a manifest strabismus and or amblyopia with no demonstrable binocular vision. Therefore it is further possible that a lack of vergence eye movements could contribute to the lack in tOKN.

In particular, if the patients' cyclovergence system has had impaired development then the subject will not be able to maintain binocular alignment when viewing torsionally disparate images. The cyclovergence system represents one component of an individual's torsional image control system, if this system is at fault, it may also result in impairment when viewing torsional field motion. Absent vergence, however, cannot completely be used to explain our findings. This is because some of the strabismus patients in both groups demonstrated a tOKN response (n = 4 in the dominant eyes, n = 8 in the non-dominant eyes).

It would be of interest to investigate further whether patients who acquired strabismus in adulthood with previously aligned eyes and normal vergence would also demonstrate a reduction in tOKN gain.

6.5.4. Comparison across OKN directions.

The results of comparing tOKN to hOKN and vOKN were inconclusive as there did not appear to be any significant correlation between the magnitudes of optokinetic

nystagmus generation in all three directions of rotation. There was a small (but non-significant) trend when comparing strabismus patients in vOKN and tOKN directions. For the dominant eyes, of the nine patients that demonstrated a higher vertical asymmetry index (upwards stimulation greater than downward, AI > 0.5), six also demonstrated a tOKN response. For the non-dominant eyes, the four patients who demonstrated a vOKN asymmetry (AI > 0.5) were also four of the five patients that demonstrated a tOKN response. Further investigation is indicated to substantiate if there is a link between torsional and upward OKN.

Previous papers comparing horizontal and vertical axes of rotation in patients with strabismus describe no definite correlation. A general trend has been observed in that patients with poor horizontal OKN do not have correspondingly poor vOKN (Garbutt *et al.*, 2003b). Others, looking at normal subjects noted the mean gain in vOKN to be the same as hOKN (Baloh *et al.*, 1983).

6.5.5. Cause of OKN asymmetry

The up-down (up greater than down) asymmetry in normal subjects has been attributed to the *delayed* OKN system, which is considered to be a peripheral vision mediated system (Murasugi & Howard, 1989b). Murasugi & Howard (1989b) found that when a 6° degree occlusive band was introduced into a vOKN stimulus moving at 50°/s and 70°/s, an increased asymmetry occurred due to a decline in downward OKN gain. When the peripheral stimulus was occluded leaving a central only stimulus (10° by 6°), the response to upwards and downwards stimulation became symmetrical in both directions, even though gains reduced. This suggests that the peripheral stimulation dominates the

delayed OKN system and causes the vOKN asymmetry, although they only performed this study on three subjects.

The tOKN system as we have suggested earlier in experiments 2 and 3, is not influenced by a pursuit mechanism because we have little capacity to make voluntary torsional eye movements (Thilo *et al.*, 1999). Consequently, it relies on a purely reflexive non-pursuit mechanism for which peripheral field stimulation appears to be significant contributor. This may well explain the absence of an asymmetry in response in normal volunteers and a more "all or nothing" response in patients with strabismus.

Vertical OKN asymmetry has also been explained by inputs from the otoliths of the vestibular system (Ogino *et al.*, 1996) since natural pitch and roll head movements cause reorientation of the otoliths relative to gravity (Matsuo & Cohen, 1984).

Valmaggia *et al*.,(2003) have attributed the presence of a horizontal OKN asymmetry to the level of binocularity present. A significant horizontal OKN asymmetry was only found in subjects with no binocularity. Studies done in monkeys have identified the loss of binocular cells in the nucleus of the optic tract (NOT) as a cause for the nasalward asymmetry (Mustari *et al.*, 2001; Tusa *et al.*, 2001; Tusa *et al.*, 2002). This results in a reduction of cortical input from the ipsilateral eye meaning that input from the contralateral eye, which responds only to nasalward stimulation, dominates the response. Furthermore, the areas of that normally provide binocular input to the NOT, the middle temporal (MT) visual area and medial superior temporal (MST) in the visual cortex have been shown to be affected when strabismus is surgically induced in infant monkeys in the first two weeks of life (Mustari *et al.*, 2001; Tusa *et al.*, 2001; Tusa *et al.*, 2002). It is

suggested the reported loss of binocularity would limit the influence they have upon the NOT.

As discussed earlier, previous findings in artificially induced disparity in normals suggest that tOKN is also affected by binocular or disparate input (Washio *et al.*, 2005). Although we know there is no pursuit involvement in torsional eye movements it could be the development of binocular cortical motion areas driving tOKN that are affected by the presence of strabismus in early childhood. In particular, one area of the MST region has been found to contain neurons that respond to large field torsional motion (Tanaka & Saito, 1989).

No work has been done with respect to identifying the neurophysiological or neuroanatomical basis of vertical and torsional OKN asymmetries after the interruption of normal binocular vision development.

7. Experiment 5: tOKN in infantile nystagmus

7. Experiment 5: tOKN in infantile nystagmus

7.1. Patient recruitment

Sixteen patients (male: 13, female: 3) aged between 18 and 49 years (mean age: 37.1 years, SD: 9.8) with infantile nystagmus (IN) were used in this experiment. All patients were recruited from hospital ocular motility clinics at the Leicester Royal Infirmary, University Hospitals of Leicester NHS trust or from research clinics held at the University of Leicester. Patients were given an information sheet to read and informed written consent was given prior to taking part in the study.

Full orthoptic and ophthalmological and optometric examination including visual acuity testing (Snellen), cover test, binocular vision (Bagolini, Lang, Frisby and TNO) was performed. Slit lamp examination of the anterior and posterior segment (after dilation) to rule out any fundus abnormality was performed. Ishihara's test (Kanehara and co, Ltd) was used to detect / rule out colour vision abnormalities. Electrodiagnostic testing including electroretinogram and visual evoked potential to detect/rule out retinal disease and albinism was performed by the medical physics department, Leicester Royal Infirmary according to the International Society for Clinical Electrophysiology of Vision (ISCEV) standards.

Table 7.1 shows the clinical characteristics of all patients used in this experiment. Seven of the sixteen patients had idiopathic nystagmus and the remaining nine patients had nystagmus secondary to other causes, i.e. albinism (n=5), ocular cutaneous albinism (n=2), achromatopsia (n=1) and optic nerve hypoplasia (n=1).

				Visual Acuity				
ID	**Age**	**Sex**	**Diagnosis**	**Right**	**Left**	**Orthoptic Status**	**BV**	**Head Posture**
N1	31	F	IIN	6/24	6/24	Orthophoria	600"	Chin Depression/ Tilt R/L
N2	25	M	OC Albinism	6/18+2	6/18-1	RE esotropia	nil	Face turn L
N3	44	M	Albinism	6/36+1	6/36+1	RE esotropia	nil	Chin Depression
N4	48	M	IIN	CF	6/9-1	RE esotropia	nil	nil
N5	18	M	OC Albinism	6/18	6/18	Orthophoria	nil	nil
N6	25	F	IIN	6/9-2	6/9	Orthophoria	85"	nil
N7	43	M	Albinism	6/12-1	6/12+2	Orthophoria	55"	Face turn R /Head bobbing
N8	34	M	IIN	6/6	6/9	Orthophoria	55"	Chin Elevation/ Face turn L
N9	46	M	Albinism	6/9+1	6/9-2	LE exotropia	nil	Face turn R
N10	49	M	Achromatopsia	6/60	6/60	RE esotropia	nil	nil
N11	34	F	Albinism	6/24	6/18-2	Orthophoria	85"	nil
N12	46	M	Albinism	6/18-1	6/18	Esophoria	600"	Face turn L
N13	45	M	IIN	6/12+1	6/12	Orthophoria	215"	nil
N14	42	M	IIN	6/19-1	6/12-2	Esophoria	150"	Face turn R
N15	39	M	IIN	6/12+1	6/15	Orthophoria	85"	nil
N16	25	M	Optic nerve hypoplasia	6/60	6/60	LE exotropia	nil	Int Face turn R

Table 7.1 *Clinical characteristics of all infantile nystagmus patients used in experiment 5.(Age(yrs, F= female, M= Male, Visual Acuity (snellens), BV = binocular vision, IIN, idiopathic infantile nystagmus OC= ocular cutaneous, CF= counting fingers, RE= right eye LE= left eye, (")= seconds of arc*

Strabismus was present in 6 of the 16 patients. (N2, N3, N4, N9, N10 and N16), the remaining 9 out of 10 patients demonstrated good binocular vision levels in the presence of their infantile nystagmus.

7.2. Procedure

Eye movement recordings were performed using the *Strabs* system as described in sections 2.2 and 5.1. Patients' spontaneous nystagmus was measured by asking them to look at a target at primary position binocularly and with each eye covered. An online calibration was performed monocularly in patients with a manifest strabismus and binocularly in patients without any manifest strabismus with the same target as described for experiment 3 section. Targets rotating at 40°/s and 400°/s in clockwise and anticlockwise directions were used to stimulate tOKN using the same method as described in experiment 3.

7.3. Data analysis

Peak to peak nystagmus amplitudes and frequency were analyzed manually in all patients using Spike 2 software program scripts for when the patients viewed the primary position target. Torsional OKN was analyzed using the same method as described in section 2.2.

7.4. Results

7.4.1. Original recordings

Figure 7.1 shows original torsional eye recordings in a patient with idiopathic infantile nystagmus (IIN) in the primary position (PP) and in response to tOKN stimulation in clockwise (CW) and anticlockwise (ACW) directions. This patient displayed no torsional component to their nystagmus in their PP waveform and there was also an absence of any tOKN response in both directions.

Figure 7.1. *Original torsional eye recordings in the primary position (PP) and in response to tOKN stimulation in clockwise (CW) and anticlockwise (ACW) directions. Arrows indicate artefact caused by blinks / lid covering iris.*

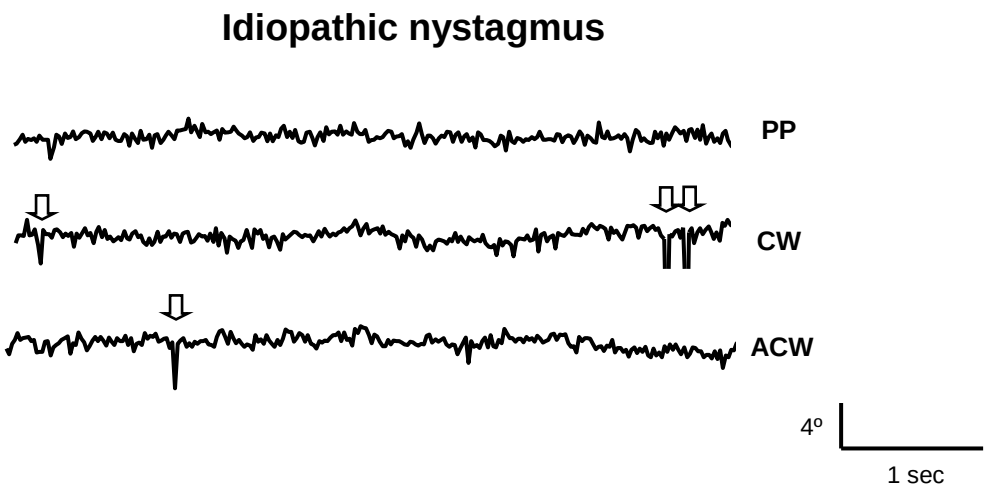
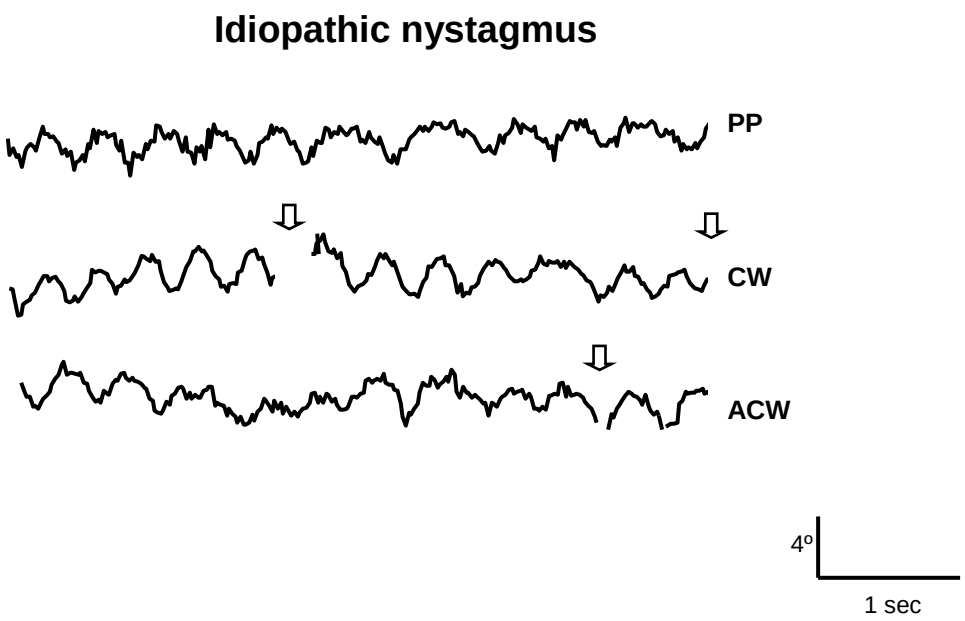


Figure 7.2 shows original torsional recordings in another patient with IIN. This patient displays a pendular nystagmus waveform in PP. There is no change in the patients PP waveform when the patient views a tOKN stimulus in the clockwise and anticlockwise directions.

Figure 7.2. *Original torsional eye recordings in the primary position (PP) and in response to tOKN stimulation in clockwise (CW) and anticlockwise (ACW) directions. Arrows indicate artefact caused by blinks / lid covering iris.*



Figures 7.3 shows original recordings in a patient with infantile nystagmus (IN), secondary to achromatopsia. This patient displays a minimal torsional nystagmus in the PP. A clear tOKN waveform is present in the clockwise direction (CW) which is consistent with the direction of the rotation of the stimulus. There is no response demonstrated to anticlockwise (ACW) stimulation.

Figure 7.4 shows original recordings of a patient with IIN. The patient has a pendular torsional nystagmus in the primary position that disappears on tOKN stimulation to reveal a tOKN response in both anticlockwise and clockwise directions of rotation.

Figure 7.3. *Original torsional eye recordings in the primary position (PP) and in response to tOKN stimulation in clockwise (CW) and anticlockwise (ACW) directions. Arrows indicate artefact caused by blinks / lid covering iris.*

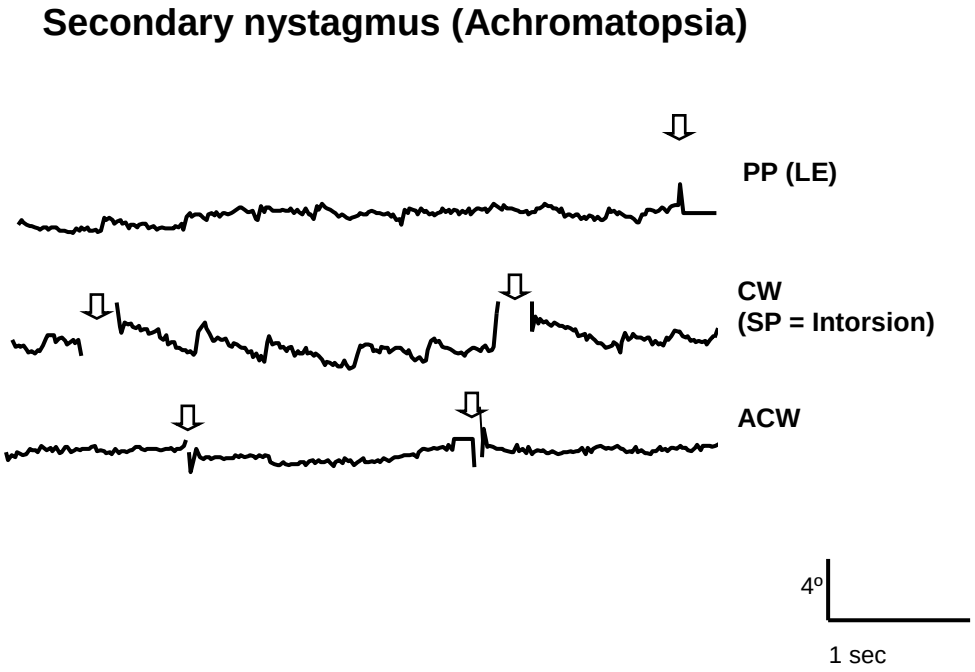
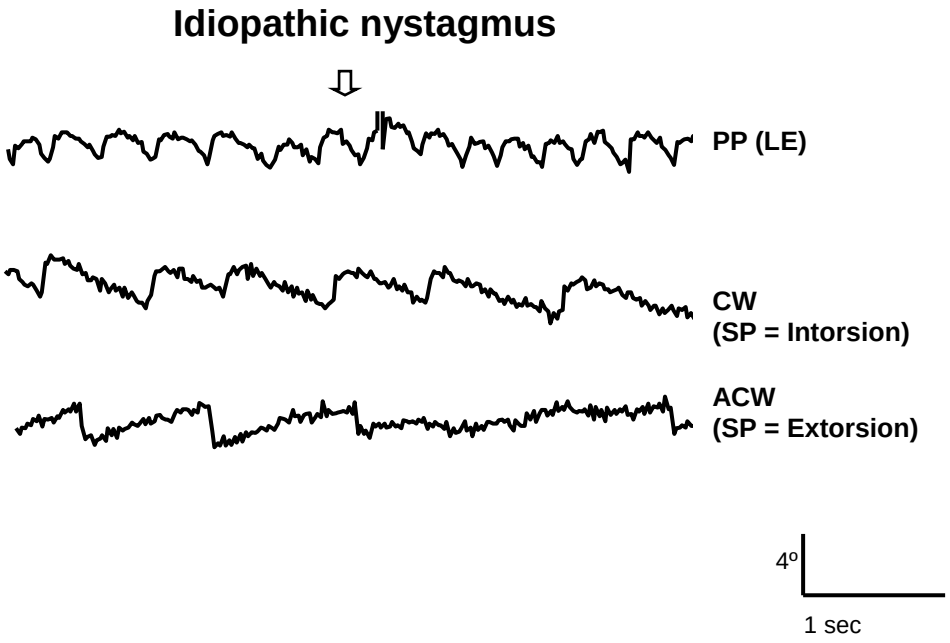


Figure 7.4. *Original torsional eye recordings in the primary position (PP) and in response to tOKN stimulation in clockwise (CW) and anticlockwise (ACW) directions. Arrows indicate artefact caused by blinks / lid covering iris.*



All nystagmus amplitudes and frequencies are shown in Table 7.2 for all axes of rotation for all patients with infantile nystagmus. Eight of the sixteen patients had a torsional component to their nystagmus (patients N1 to N8). In patient N4, this was the major nystagmus component of his nystagmus. All patients had manifest nystagmus in the primary position which was jerk in waveform (n=8) or a combination of pendular/jerk (n=8).

Torsional OKN was absent in 13/16 patients tested as no tOKN response was identifiable to either stimulus velocity in clockwise or anticlockwise directions. Torsional OKN was present in the remaining 3 patients (1 secondary, 2 idiopathic).

ID	Diagnosis	Type	Horiz. Amp (º)		Horiz. Freq (Hz)		Tors. Amp (º)		Tors. Freq (º)		tOKN
			RE	LE	RE	LE	RE	LE	RE	LE	
N1	IIN	P	3.12	3.54	3.43	2.87	1.99	1.06	3.65	3.65	✓
N2	OC Albinism	P&J	8.26	6.96	2.40	2.39	2.74	0.69	2.15	4.13	×
N3	Albinism	J	9.02	10.92	3.81	4.23	2.29	1.65	3.25	3.25	×
N4	IIN	J	3.75	3.11	3.14	3.05	5.13	4.32	2.50	2.50	×
N5	OC Albinism	P	5.28	4.98	2.24	2.35	1.77	1.74	1.71	1.71	×
N6	IIN	P	7.83	11.65	2.00	2.00	2.31	5.13	2.00	2.00	×
N7	Albinism	J(H)P(T)	4.17	3.35	3.58	1.89	2.02	2.10	3.58	2.62	×
N8	IIN	P	4.54	4.62	5.22	5.22	4.05	2.55	5.22	5.22	×
N9	Albinism	J	2.87	3.79	2.29	2.21					×
N10	Achromatopsia	P&J	0.72	0.86	5.41	3.63					✓
N11	Albinism	J	2.91	2.38	3.24	3.16					×
N12	Albinism	J	7.69	7.93	3.18	3.17					×
N13	IIN	J	4.64	4.43	3.55	2.64					×
N14	IIN	P&J	1.40	1.52	7.21	7.05					✓
N15	IIN	P	1.91	1.82	3.14	3.16					×
N16	Optic nerve hypoplasia	J	1.54	1.43	5.60	3.04					×

Table 7.2 *Infantile nystagmus amplitude and frequencyin all patients. Pateints N1-N8 had a torsional(Tors) component in addition to their horizontal (Horiz) nystagmus.(IIN,=idiopathic infantile nystagmus, OC= ocular cutaneous, Type= waveform (P= pendular, P&J= pendular and jerk, J=jerk)* ✓= *tOKN present* ×= *tOKN absent)*

Table 7.3 shows the MSPV of all three patients that displayed a tOKN response with slow phase in either intorsion (Int) and extorsion (Ext) directions at either stimulus velocity. Comparative normal values are also shown. Two of these three patients only displayed a response at 400°/s. One patient (N1) displayed a higher than normal MSPV in the intorsion direction.

Table 7.3. *Torsional OKN MSPV in infantile nystagmus patients that were responders. Extorsion (Ext) and Intorsion (Int) directions of stimulation are shown with stimulus velocities in brackets for each direction of response.*

		Torsional OKN (MSPV(º/s))			
ID	**Diagnosis**	**Ext (40º/s)**	**Ext (400º/s)**	**Int (40º/s)**	**Int (400º/s)**
N10	Achromatopsia	×	×	×	2.52
N14	IIN	×	2.60	×	3.43
N1	IIN	×	2.85	7.97	6.19
Normals (15 age matched)		1.53	2.07	1.31	2.03

7.5. Discussion.

We have investigated the tOKN response in patients with infantile nystagmus (IN) and found, for the first time, a high incidence of an absence in tOKN response in 81% of all patients. Of the three patients that showed a response, a higher than normal stimulus velocity was required to elicit the response. There was no reversal of the response noted as has been noted by previous studies investigating the horizontal OKN response in IN (Halmagyi *et al.*, 1980).

7.5.1. How does this compare with previous work?

The interaction of pre-existing nystagmus to the OKN response in the horizontal and vertical direction has been previously investigated. Abadi & Dickinson (1985) looked at a group of 21 patients with congenital nystagmus when viewing a large display eliciting horizontal and vertical OKN. Although DC electro-oculography was used, in which vertical eye movements can be difficult to measure due to lid artefacts, they examined a group of patients with idiopathic nystagmus and nystagmus due to albinism. When OKN was stimulated in the same plane as the nystagmus oscillation, all of the 21 subjects demonstrated a gaze modulated response, in which the *fast phase* of the OKN response occurred in the same direction as stimulus movement. This is the opposite that would be expected during OKN stimulation as the *slow phase* normally moves in the same direction of stimulus motion. They did, however find that the vertical OKN response in these subjects exhibited a normal 'saw tooth' appearance, although the asymmetry found in normal subjects (upward response greater than down) was not replicated. This allowed them to conclude that OKN in IN was only affected in the same plane as the nystagmus oscillation agreeing with previous studies (Jung & Kornhuber, 1964; Abadi *et al.*, 1982).

The findings of our study, however, show that this cannot be extended to the torsional plane. We discovered that, of the 8 patients with no torsional component to their nystagmus, 6 did not display any tOKN response (Table 7.2). Similarly, of the patients who did have a torsional component to their nystagmus, 7 of the 8 had an absence of tOKN. The gaze modulated response was not seen in the one patient with a torsional component to her nystagmus that *did* demonstrate tOKN**.** This patient demonstrated a clear saw tooth wave-form that was consistent with the direction of rotation of the stimulus

which overrode her spontaneous torsional nystagmus as shown on Figure 7.4. An additional component of gaze modulation has been described whereby the direction that OKN stimulation occurred in elicited the nystagmus normally occurring in the same direction of gaze. For example, rightward moving OKN stimulation elicited the same nystagmus that normally occurred in right gaze and visa versa (Abadi & Dickinson, 1985). The pre-existing torsional nystagmus in our subjects with a torsional component to their nystagmus was not changed when the tOKN stimulus rotated in either clockwise or anticlockwise directions. However, as we do not have voluntarily altering *torsional* gaze positions in the same way we have horizontal and vertical gaze positions, this type of modulation cannot really be tested.

7.5.2. Influence of head posture

One factor that could contribute to alteration of torsional eye position is the presence of a head posture, more specifically a head tilt to achieve ocular counterrolling of the eyes in the opposite direction to the head posture. This would occur if the patients had an area in which the nystagmus dampened in the torsional meridian, in effect a torsional 'null' zone. Of the nine patients in our study that demonstrated a head posture as shown in table 7.1, one (patient N1) had a head tilt in combination with a chin depression. This patient did have a torsional component to their nystagmus which was smaller than her horizontal nystagmus component (for the RE, 1.99º torsional nystagmus versus 3.65º horizontal nystagmus). This patient also demonstrated a tOKN response. Further investigation with a large number of patients that present with head tilts and torsional

nystagmus would need to be done to clarify whether any effect on the torsional component to the nystagmus was found in the presence of a head tilt.

7.5.3. Mechanisms behind IN

Kommerell & Mehdorn (1982) have proposed a theory regarding the cause of infantile nystagmus. They suggest a basic OKN abnormality that would cause congenital nystagmus in the direction of the abnormality. For example, a congenital *horizontal* OKN defect would result in *horizontal* infantile nystagmus. They argue that an absent or defective OKN system would result in an unsteady retinal image causing the eyes to oscillate spontaneously resulting in nystagmus. This theory cannot explain why patients in our study that had no tOKN *did not* demonstrate a torsional component to their nystagmus (n=7/8) (Table 7.2).

This theory also does not explain why the infantile nystagmus can be present in more than one plane of oscillation, i.e. can have a combination of horizontal, vertical and/or torsional components. Eight patients in our study had torsional and horizontal nystagmus in combination. In one study, Averbuch-Heller *et al.* (2002) showed that in a group of 13 patients with congenital nystagmus, the torsional nystagmus component ranged from 8.16% to 94.42% (median 32.94%) of the peak to peak magnitudes found and rightward upward and clockwise coincided in 10 subjects. In our patients the torsional nystagmus component ranged from 9.92% to 137% of the horizontal peak to peak amplitude (median = 39.5%).

The presence of torsional infantile nystagmus has been explained using:

(i) **Listing's Law:** Primary position, as defined clinically, may be a few degrees off-set from what is defined as Listing's primary position. It has been shown that torsion is induced during horizontal rotations of the eye (Ferman *et al.*, 1987b, a). Therefore, infantile nystagmus ranging from 1-20º may induce 0.01º to 4º of torsional peak to peak amplitudes (Averbuch-Heller *et al.*, 2002).

(ii) **Central torsional control system:** Averbuch-Heller *et al*. (2002) report 2 of their subjects having a different torsional nystagmus waveform to their horizontal nystagmus waveform which they felt argues against a common cause for both types of nystagmus.

Explanation (i) has been discounted by Averbuch- Heller *et al.* (2002) who found torsional nystagmus greater than would be predicted to account for Listing's torsion. Consequently, the instability of torsional control (i) is a more accepted explanation. An abnormality of central torsional control would also explain the results of our experiments with IN patients since the hypotheses relating to OKN abnormalities proposed by previous authors do not provide adequate explanation (Abadi & Dickinson, 1985).

7.5.4. Torsional OKN characteristics in IN.

Of the three patients in our study that did exhibit a tOKN response, two of these three consistently only demonstrated a response at the higher stimulus velocity of 400°/s. An explanation regarding the high level of undetectable tOKN in our patients could be that if tOKN gain in these patients is so low that it is indistinguishable from their IN waveform. We know that the tOKN response is much smaller response than hOKN and vOKN

(Collewijn *et al.*, 1985; Cheung & Howard, 1991; Seidman *et al.*, 1992; Morrow & Sharpe, 1993; Suzuki *et al.*, 2000) in which a reduced gain may be easier able to be detected. The VOG *Strabs* system records at 50 Hz, so the normally occurring noise in the system could add to the problem of being able to detect a tOKN trace with manifest nystagmus. A higher resolution torsional recording system could avoid this experimental limitation.

The gain and MSPV of the tOKN found in the patients who were responders in our study was not dissimilar to normal values in age-matched subjects. Yee *et al*. (1980) looked at the horizontal OKN response in subjects that were found to have a normal OKN waveform (11/28 idiopaths and 7/18 secondary). The patients were found to have a low hOKN gain ranging from 0.19 to 0.38 over three stimulus velocities compared to the highest normal gain from control subjects of 0.88.

Six of the sixteen patients used in our experiment demonstrated strabismus in addition to their infantile nystagmus. Five of these patients demonstrated no tOKN response, therefore this additional factor cannot be ruled out as a cause for the absent tOKN in these patients. The converse however was also noted, as of the three patients that did demonstrate a tOKN response, one (N10) did have strabismus and a large proportion of patients (n=8) that had no clinically demonstrable strabismus also displayed no tOKN response.

Recently mutations in a novel gene called *FRMD7* (Xq 26.2) (NYS1) have been found which are a major cause of X-linked idiopathic congenital nystagmus (Tarpey *et al.*, 2006). The OKN responses of some obligate non-affected carriers of this mutation were found to be subnormal when compared to normal which may further suggest an

association between abnormal OKN systems and infantile nystagmus (Thomas *et al.*, 2008).

8. General Discussion

8. General Discussion

The torsional optokinetic response (tOKN) was systematically examined in the normal population and patients with ocular motor disorders.

A linear relationship between stimulus velocity and tOKN slow phase velocity was found when a sectored disc stimulus, rotating in clockwise and anticlockwise directions, was varied in radial speed from 3°/s to 1000°/s. This is the first time the optimum gain and slow phase eye velocity for tOKN have been established, thus enabling other researchers to apply these findings to their investigations (Lopez *et al.*, 2005a). Torsional OKN also showed a brisk response to peripheral field stimulation in the same group of subjects. When only 15% of the stimulus was presented as an annulus in the periphery, normal subjects responded with 50% of the gain of that observed for the full stimulus. In 30 normal subjects aged between 19 and 72 years, a significant increase with age in the proportion of subjects demonstrating an absent tOKN was found. This is the first time an aging effect has been discovered in relation to tOKN.

OKN responses in strabismus patients demonstrated consistent asymmetry in horizontal and vertical directions. However, a significantly higher incidence of absent tOKN, in both intorsion and extorsion directions, was observed for the first time for strabismics in comparison to control volunteers. Similarly, tOKN was present in very few patients with infantile nystagmus with 81% of patients not demonstrating any response for a variety of stimulation velocities and directions.

Overall, I am able to deduce that the tOKN system demonstrates characteristics that are similar and different to that observed along the horizontal and vertical meridians. In the horizontal and vertical directions, it is believed that at slower stimulus velocities, a

pursuit mechanism mainly contributes to the OKN response (described as the *early* OKN) whereas at higher velocities a more reflexive OKN system is utilized (Wei *et al.*, 1992; Fuchs, 1993). Since torsional OKN is not influenced by a pursuit mechanism, as we have little capacity to make volitional torsional eye movements, this would suggest a purely reflexive system must be acting which, demonstrates similarity to the *late* OKN system.

8.1. Pursuit Influence

The role of pursuit could explain some of the observations in experiments 2 (effect of stimulus area) and experiment 3 (normal aging) with respect to the tOKN response. Previous authors have shown that horizontal and vertical OKN show a small decline with age (Spooner *et al.*, 1980; Simons & Buttner, 1985; Kato *et al.*, 1994; Valmaggia *et al.*, 2004) (Demer, 1994). However, pursuit measures show less deterioration compared to OKN measures in elderly subjects (Kerber *et al.*, 2006). Therefore, it is possible that the rate of hOKN and vOKN decline with age may be slowed due to the contribution of pursuit to the response. In our study, the reason why there is a sharp decline in tOKN with increasing age may be because of the lack of pursuit input to this response.

Even though there are differences in the contribution of the pursuit component to tOKN and hOKN responses, there may still be common mechanisms of activation to tOKN and hOKN. When varying the amounts of central and peripheral field stimulation in experiment 2, we found that peripheral field stimulation was able to generate a large tOKN response. Similarly previously studies into horizontal OKN (Abadi & Pantazidou, 1997; Valmaggia & Gottlob, 2002) have shown that the *rise time,* used as a marker for eliciting early OKN, was no different when viewing a central field stimulus of 20º diameter or

when the central field was occluded. This indicated that central and peripheral stimuli activate common mechanisms to elicit the early component of OKN (Abadi & Pantazidou, 1997).

Furthermore, the horizontal OKN response was not significantly affected in patients with pathological central scotomas.

8.2. Stimulus characteristics and tOKN generation

The radial nature of the tOKN stimulus results in a variation in the linear velocity of the rotating sectors, with an increase in linear velocity with increasing eccentricity from the point of rotation (as highlighted in the methods section 2.3, page 76). Consequently, linear motion in the peripheral field is much more rapid than motion in the central field. In contrast, for the horizontal and vertical OKN stimuli used, there is a constant linear velocity in both the central or peripheral field. This could explain the results of experiment 2 where it was observed that the peripheral field had a relatively stronger effect on generating a tOKN response in comparison to the central field.

The experimental paradigm where we do see the linear velocity of the tOKN stimulus being constant is when an annular stimulus, stimulating the peripheral field is used. This stimulus has variation in its central portion but always maintains a constant peripheral component. It appears from the results of experiment 2 that this type of stimulus was well suited to tOKN generation. This difference in linear and radial velocity in the tOKN stimulus could serve as an explanation to why tOKN seems to best suited to full field and peripheral stimulation. Furthermore, the results from these experiments could

also be interpreted as a demonstration of characteristics of the OKN response in general; being most suited to fixed linear stimulus velocity stimulation.

8.2.1. Comparison to neurophysiological evidence

The previous literature outlining the neurophysiological basis to torsional visual motion processing corroborates our results describing the normal response characteristics in tOKN. We found that the tOKN response responds proportionally to variation in stimulus velocity, with a symmetrical response in clockwise and anticlockwise directions and a brisk response to peripheral stimulation. This corresponds well with the types of cells that have been found that respond to torsional visual motion. These neurons have been located by Saito *et al.* (1986) in the dorsal part of the medial superior temporal visual area (MST). Two types of cells were highlighted that responded to torsional field motion, termed *R1* and *R2* cells. An equal amount were found to respond to either stimulus direction (i.e. clockwise and anticlockwise) and responded optimally at stimuli that exceeded 40º in diameter. In addition an annular stimulus, with a missing central portion, evoked a good response from these rotation cells.

Two types of response were observed in relation to varying stimulus velocity in these MST rotation cells. Interestingly, *R1* cells were found to respond to a limited range of stimulus velocities, in contrast *R2* cells responded to a whole range of speeds (Tanaka & Saito, 1989).

8.3. Absent tOKN

Results of experiments 3, 4 and 5 demonstrated diminished or absent tOKN with increasing age, in the presence of longstanding strabismus and infantile nystagmus, respectively. One common factor that could account for this finding is related to the small magnitude of tOKN response in comparison to hOKN and vOKN, as found in experiments 1 and 2 (Farooq *et al.*, 2004). Since the response falls much closer to threshold compared to horizontal and vertical OKN, it may be more sensitive to the aging process, and in the presence of strabismus and infantile nystagmus.

Previous work in monkeys has identified the loss of binocular cells in the nucleus of the optic tract (NOT) as a possible cause for hOKN asymmetry (Mustari *et al.*, 2001; Tusa *et al.*, 2001; Tusa *et al.*, 2002). Furthermore, it has been found that the cortical areas (the middle temporal (MT) and medial superior temporal (MST) cortex) that normally provide binocular input to the NOT are affected when strabismus is induced in infant monkeys (Mustari *et al.*, 2001; Tusa *et al.*, 2001; Tusa *et al.*, 2002). Tran *et al.* (1998) have shown that in aging subjects the motion detection and perception areas affected could be occurring at different cortical and subcortical levels The cortical areas affected could be similar to those found in the presence of strabismus in monkeys.

As stated above, activity in the dorsal part of MST region is associated with large field torsional motion (Tanaka & Saito, 1989). Therefore, it is possible that binocular cortical motion areas driving tOKN could be affected in the presence of strabismus and aged subjects. Furthermore as strabismus has a close association with infantile nystagmus (n=6 patients had strabismus in the presence of infantile nystagmus), similar cortical motion areas could be affected in this subject group too.

8.3.1. Influence of vergence

Normally, binocular vision development would result in vergence eye movements to maintain binocular vision at different distances. Longstanding strabismic patients, by definition, have no binocular vision and in turn limited vergence eye movements. Similarly, it has also been shown that with increasing age our ability to perform horizontal vergence eye movements is also diminished (Rambold *et al.*, 2006). If cyclovergence is affected in a similar manner then it may be possible that an individual's ability to deal with torsional field motion could also be affected. All strabismus patients in our study had no demonstrable binocular vision; therefore it is possible that a lack of vergence eye movements could also contribute to the absence in tOKN. Furthermore if the cyclovergence system, which represents one component of visual processing in the torsional plane, has not developed normally due to a lack of cortical development resulting from strabismus, this could result in impairment when viewing torsional field motion.

Further understanding of the role of vergence eye movements on OKN and in particular tOKN has been gained from work in which artificial disparities are induced in normal subjects. Washio *et al*. (2005) induced horizontal disparities in subjects viewing torsionally rotating stimuli and measured their tOKN response. This required subjects to perform horizontal vergence movements to overcome the disparity. Interestingly, in these patients it was found that optimum tOKN was elicited in all zero disparity conditions, i.e. when no additional horizontal vergence from that would normally be occurring, was induced.

This suggests that our 'resting' or tonic state of horizontal vergence is best suited to respond optimally to torsional motion. It is yet to be determined whether artificially

induced cyclodisparities requiring cyclovergence eye movements to be made, have any effect the tOKN response. This suggests an avenue of further investigation.

In comparison to the strabismic patients, a higher proportion of patients in experiment 5 with IN demonstrated good binocular vision (N=8). However, these subjects also demonstrated absent tOKN. Therefore, it is possible that in the presence of IN, although this is also a disorder of the oculor-motor system, other mechanisms are at fault that prevent the manifestation of a normal tOKN response.

8.3.2. Visual perception and compensation for torsion

A further explanation that could explain the absence or lack of detection of the tOKN responses in the aged, strabismic and infantile nystagmus subjects could be related to the level of perceptual compensation for a rotating stimulus. We know from other human torsional eye movements such as cyclovergence and ocular counterrolling, that a proportion of the response is thought to be a sensory component in addition to the normally occurring motor component. For cyclovergence, subjects have been shown to be able to resolve approximately 10º of torsional disparity through sensory mechanisms (Kertesz & Jones, 1970). Similarly, ocular counterrolling has been shown to account for only 10% of head movement, suggesting that mostly a sensory adaptation to change in torsional position must occur (Collewijn *et al.,* 1985; Averbuch-Heller *et al.,* 1997). The subjects that demonstrate absent tOKN in our study may well perceive the stimulus as rotating (all subjects reported this in these experiments), but be unable to produce the motor command to elicit the eye movement. The experiments in which *filling-in* was

reported by normal volunteers, without any effect on the eye movements generated, may indicate such perceptual mechanisms to be occurring within the tOKN response.

9. Conclusion

In response to the aims of this thesis I am able to conclude that the torsional optokinetic response (tOKN) in humans shows characteristics that are both similar *and* different to OKN in horizontal and vertical directions.

1) We systematically investigated the relationship between stimulus velocity and the gain of tOKN by using a large range of stimulus velocities to establish the limit and optimum level of response. A significant relationship between stimulus velocity and eye movement was shown for the first time with tOKN responses evident for a large range of stimulus velocities. This will enable future researchers to compare findings to our normative data.

2) We examined the effects of central and peripheral stimulation on the tOKN response by varying the size of the central and peripheral field. A brisk response to peripheral field stimuli common to what has previously been found in the horizontal OKN system suggests similar activation mechanisms.

3) We investigated the *filling-in* response when central portions of the stimulus were occluded and it was found that the perceptual effect of filling-in while looking at a tOKN stimulus had no change on the tOKN eye movements generated.

4) We examined the effects of normal aging on the tOKN response and have shown for the first time that aging dramatically affects the tOKN response. The tOKN response appears

to be less robust in dealing with the effects of aging when compared to OKN in other directions.

5) We investigated the tOKN response in adults with longstanding strabismus due to Essential Infantile Esotropia Syndrome (EIES) and Childhood Strabismus (CS) in comparison to hOKN and vOKN. The response in horizontal and vertical directions produced consistent patterns of asymmetry that were the same in dominant and non-dominant eyes. The tOKN response appears symmetrical in normal subjects similar to hOKN response; however we have shown for the first time, there is a high incidence of absent tOKN response in contrast to hOKN and vOKN in the same group of patients. Possibly the lack of development in the binocular cortical structures that respond to torsional motion could explain these findings.

6) In patients with Infantile Nystagmus (IN) there was also a high incidence of absent tOKN response similar to the strabismic patient, which has not been previously described. Earlier mentioned theories regarding defective OKN responses in IN do not explain the findings of our study. This suggests that the tOKN system is possibly modified in a different way or has less capacity to be modified when compared to the hOKN and vOKN systems in the presence of IN.

9.1. Future Studies

Given the changes observed in infantile forms of strabismus and nystagmus, further investigation into tOKN responses in acquired forms of strabismus and nystagmus would be of interest. This would enable us to compare to the results we have from patients with infantile ocular movement abnormalities and acquired forms. Patients with pathological central scotomas could also be investigated to see if any difference is noted in their tOKN response. Pharmacological treatment has recently been shown to affect infantile nystagmus (McLean *et al.*, 2007). It would be of interest to investigate whether pharmacological treatment influences the torsional component of infantile nystagmus. This could provide us with more information regarding the mechanisms underlying torsional nystagmus.

There has been no work on the development of the neurons in the presence of congenital ocular motor abnormalities or in the changes associated with the process of aging. It would be interesting to investigate how the responses in these neurons develop with age and whether this is affected by congenital ocular motor abnormalities. It would also be interesting to investigate the effects of senescence. Furthermore, given the influence of artificially induced horizontal disparities on the tOKN response, it would be of interest to investigate whether artificially induced cyclodisparities requiring cyclovergence eye movements to be made, have any effect the tOKN response.

10. APPENDICES

Appendix (A)

Publications

(A) Farooq SJ, Gottlob I, Benskin S, Proudlock FA. The Effect of Aging on Torsional Optokinetic Nystagmus. **Investigative Ophthalmology & Visual Science.** 2008; 49(2): 589-593.

(B) Farooq SJ, Proudlock FA, Gottlob I. Torsional optokinetic nystagmus: normal response characteristics. **British Journal of Ophthalmology**. 2004 Jun; 88(6): 796-802.

The Effect of Aging on Torsional Optokinetic Nystagmus

Shegufta J. Farooq,[1] Irene Gottlob,[1] Sherwin Benskin,[2] and Frank A. Proudlock[1]

Purpose. The effect of aging on torsional optokinetic nystagmus (tOKN) is unknown. The authors investigated changes in tOKN associated with aging in a group of healthy subjects.

Methods. Monocular torsional eye movements were recorded from 30 subjects between 19 and 72 years of age. Constant-velocity rotary stimuli in clockwise and counterclockwise directions were used to elicit tOKN at 40°/s and 400°/s.

Results. The number of subjects in whom tOKN could not be detected increased with age and was consistent in both directions of stimulation and at both angular velocities of stimulation.

Conclusions. tOKN appears to fail increasingly with age, in contrast to previous reports of horizontal and vertical OKN systems. This indicates that the ability to respond to rotary motion is more sensitive to the effects of aging. (*Invest Ophthalmol Vis Sci.* 2008;49:589–593) DOI:10.1167/iovs.07-0899

Torsional optokinetic nystagmus (tOKN) is an ocular motor response that occurs during viewing of a rotating stimulus. Similar to horizontal and vertical OKN responses, it consists of a slow phase in the direction of the stimulus followed by a fast phase in the opposite direction. It contributes to stabilization of the retinal images during rotary movement of the visual field. We have recently described the normal response characteristics of the tOKN response in young adults[1]; however, the effect of aging on the response has not been investigated.

In contrast, the horizontal OKN response has been widely investigated with age and has been shown to undergo a mild but significant deterioration.[2–5] This has been attributed to age-related degeneration in cortical areas responsible for motion perception and in the retinogeniculate pathway,[6] though degeneration of ocular motor areas cannot be ruled out. The effect of vertical OKN has also been investigated.[7] Similarly, OKN responses in elderly subjects have been found to be inferior to those in younger subjects.

OKN in the horizontal and vertical directions can be influenced by components of the voluntary pursuit system. Therefore, it has been postulated that the effects of aging on the pursuit system could influence the OKN system.[3] Published reports in this area generally agree that the pursuit system deteriorates with age.[3,5,7–9] tOKN, however, is purely reflexive and is not influenced by a pursuit mechanism because little or no movement occurs at the fovea when a subject fixates the stimulus.[10] It would be of additional interest, therefore, to see how the tOKN system compares with previously published results on horizontal and vertical OKN.

We examined the monocular tOKN response in a group of healthy subjects between 19 and 72 years of age by testing eye rotation in intorsion and extorsion directions in response to 40°/s and 400°/s stimulation.

Subjects and Methods

Subjects

Thirty subjects (19 women, 11 men) between 19 and 72 years of age (mean ± SD, 50.1 ± 18.1 years) were included in the study. All subjects had normal corrected visual acuity of 6/9 (20/30) or better in the viewing eye. Orthoptic examination was performed to exclude any ocular motility and binocular vision defects. All tests were performed without refractive correction or with contact lenses if refractive correction was necessary. On questioning, all subjects reported that they were free of neurologic and otologic problems. Nine of the 30 subjects were taking medication for hypertension ($n = 4$), cholesterol lowering ($n = 4$), diabetes (noninsulin-dependent diabetes mellitus, $n = 2$), or hiatus hernia ($n = 1$). Seven subjects were older than 65. None of the subjects were taking medication for depression.

Responses from the right eye were recorded unless visual acuity was less than 6/9 (20/30) or eye movement recording quality was lower than 0.5, in which case the left eye was used ($n = 3$; torsional eye movement recording quality is defined in Data Analysis). The study received local ethical approval and was performed with consent after explanation of the nature and possible consequences of the study. The study was performed in accordance with tenets of the Declaration of Helsinki.

Eye Movement Recording

Eye movements were measured in three dimensions using a video-oculography technique (VOG) at a sampling rate of 50 Hz (Strabs system; Sensomotoric GmbH, Teltow, Germany). The equipment consisted of infrared video cameras fitted to a face mask attached to the head with a rubber strap (Fig. 1). Pupil tracking was used to derive horizontal and vertical movements. A segment of the iris was tracked to measure torsional eye movements. The system has a spatial resolution of 0.03°, 0.02°, and 0.1° and a linearity of ±3.8%, ±3.2%, and ±1.4% full-scale reading for horizontal, vertical, and torsional eye movements, respectively (company specifications). The range of linear measurement was ±25°, ±20°, and ±18° for horizontal, vertical, and torsional eye movements, respectively. Noise for the setup was estimated from the torsional recordings as 0.1° to 0.2°/s root mean square for torsional angle and 0.1° to 0.15°/s root mean square for torsional velocity. The digitized ASCII file output for horizontal vertical and torsional data was converted to software files (Spike 2; Cambridge Electronic Design, Cambridge, UK) for analysis.

Each subject sat upright with the head stabilized on a chin rest placed 120 cm away from the stimulus. The height of each subject was adjusted so that the center of the stimulus and the subject's eyes were at the same level. The cameras of the VOG system were adjusted while the subject viewed the stationary stimulus so that pupil size, threshold,

From the [1]University of Leicester, Ophthalmology Group, Faculty of Medicine and Biological Sciences, Leicester, United Kingdom; and the [2]University Hospital of Leicester, NHS Trust, Leicester, United Kingdom.

Supported by the Ulverscroft Foundation.

Submitted for publication July 17, 2007; revised September 10 and October 8, 2007; accepted December 12, 2007.

Disclosure: **S.J. Farooq**, None; **I. Gottlob**, None; **S. Benskin**, None; **F.A. Proudlock**, None

The publication costs of this article were defrayed in part by page charge payment. This article must therefore be marked "*advertisement*" in accordance with 18 U.S.C. §1734 solely to indicate this fact.

Corresponding author: Frank A. Proudlock, University of Leicester, Ophthalmology Group, Faculty of Medicine and Biological Sciences, Robert Kilpatrick Clinical Sciences Building, Leicester Royal Infirmary, PO Box 65, Leicester LE2 7LX, UK; fap1@le.ac.uk.

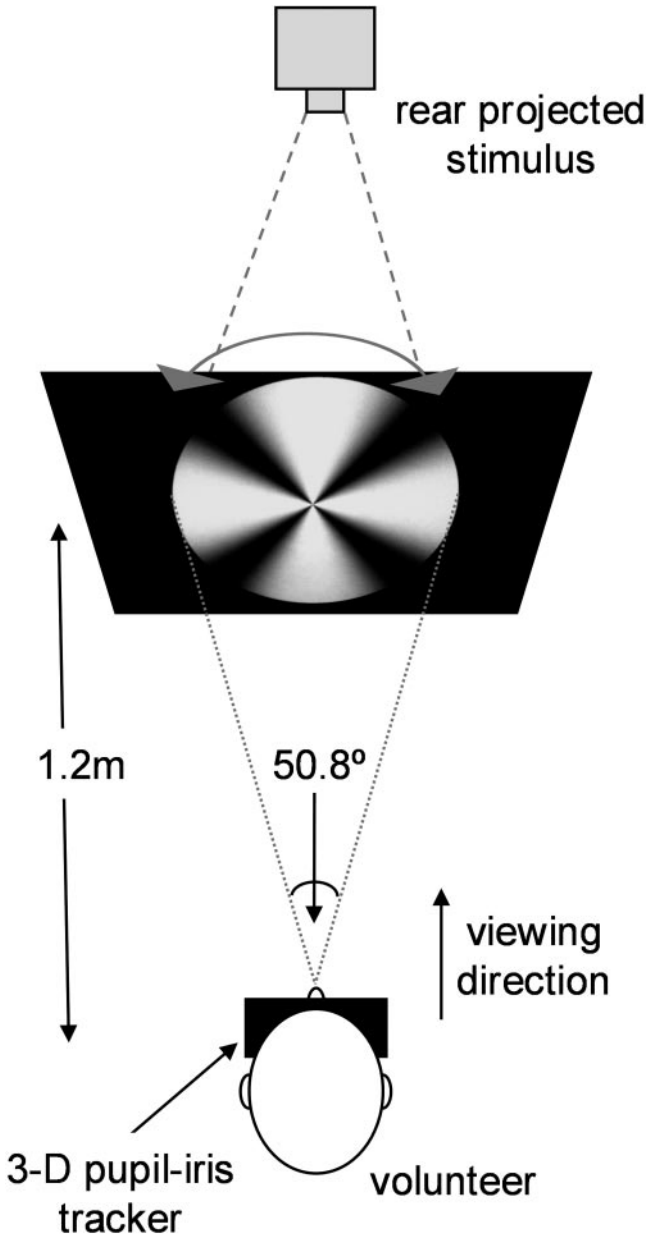


FIGURE 1. Experiment setup for recording tOKN.

and contrast levels could be set at the experimental conditions to ensure the highest quality of recording.

A five-point calibration of each eye was performed monocularly, with the nonviewing eye covered before the testing procedure began. Subjects fixated points centrally, 15° in depression, right gaze, in elevation, and left gaze. Recordings were taken monocularly, and a cover was used for the nonviewing eye during testing. Torsional measurements were calibrated within the VOG setup, determined from rotations of the iris. The torsional angle was defined with reference to the initial image measured when the experiment was set up.

The experimental stimulus was projected onto a 1.75 × 1.17-m rear projection screen using an LCD projector (resolution 1024 × 768 pixels; model EMP 703; Epson, Long Beach, CA). Stimuli were generated using a visual stimulus projector (VSG 2/5; Cambridge Research Systems, Rochester, UK) and consisted of a rotating sinusoidal grating pattern of 90° cycle size subtending 50.8° in diameter (Fig. 1). The luminance of the grating pattern varied from 0.45 to 23.0 cd/m^2, giving a luminance contrast of 96%. The stimulus revolved around its central axis at 40°/s and 400°/s in clockwise and counterclockwise directions. The subjects were asked to stare at the center of the stimulus keeping it in focus. Each stimulus was presented for 30 seconds, followed by a blank phase of 15 seconds during which the subject was asked to fixate a black screen.

Four of the subjects who showed no responses at 40°/s and 400°/s (all men; aged 56, 59, 63, and 72 years) were tested across a wider range of stimulus velocities—20°/s, 100°/s, 200°/s, 800°/s, and 1000°/s—in both directions.

Data Analysis

A section of the iris, the "signature segment," was selected from a reference video frame to include significant landmarks in the iris from which luminance levels were measured. Torsional eye position was derived from angular displacement of the defined segment. To estimate the angular displacement, the luminance levels from subsequent video frames were cross-correlated for the corresponding segment with the original signature segment. The cross-correlation value also provided a measure of correspondence between the signature segment and the subsequent image that was used as an estimate of the quality of the recording. Only data that exceeded a torsional quality of 0.5 were used for analysis (a correlation close to 1 implied the best data quality). Poor-quality data could result from an iris segment without many landmarks and changing pupil size because of altered illumination, leading to changes in the position of landmarks. They could also result when the pupil was not accurately detected because of small size or interference from surrounding ocular structures (e.g., dark eyelashes, lashes with heavy eye makeup, droopy eye lids). Subjects were instructed to "open their eyes wide" when it was considered from online displays of the eyes that it was possible the eyelids were occluding the recording. A drop in torsional quality of the data in the blank phase, caused by changing pupil size, meant that measurement of torsional optokinetic afternystagmus was unreliable. Torsional quality of the data during measurement of tOKN did not significantly change with age in the study (linear regression: $r^2 = 0.02$, $P = 0.2$).

Smoothed velocity traces of the torsional data were created using a simple five-point low-pass differentiator filter (linear). A velocity threshold of 10°/s was used as a default to determine saccades in the torsional recording. Because the level of noise varied, depending on the quality of the torsional recording, the velocity threshold could be adjusted manually (invariably reduced) to just exceed the noise level evident in the smoothed velocity trace. The mean velocity threshold selected across all subjects was 6.98°/s (SD 1.79°/s). This equates to discrimination of saccades of 0.55° or larger (determined from peak velocity/amplitude characteristics for the setup). For a mean beat frequency of 1.46 Hz (the mean of the subjects showing tOKN in this study), this approximated to a slow-phase velocity of 0.80°/s.

For subjects classified as responders, the mean velocity over a minimum of 10 slow phases from each 30-second trace was used to give the mean slow-phase velocity (MSPV) for each stimulus. Because MSPVs were not normally distributed across the subjects, median values were used for analysis. Subjects classified as nonresponders had no slow phases within the 30-second analysis section. One subject was excluded from the original study group of 31 subjects because the quality trace of the torsional segment fluctuated during testing; hence, a constant noise-free recording was difficult to achieve.

As monocular eye movements were recorded, the relative direction of rotation of the eye differed according to which eye was fixing (e.g., clockwise stimulation to the right eye produced a slow phase that extorted the right eye and intorted the left eye and vice versa). To avoid misinterpretation, the direction of the eye rotation and the velocity of the stimulus were defined in relation to intorsion/extorsion of the viewing monocular eye.

Statistical Analysis

Changes in the proportion of nonfunctional tOKN with age were analyzed using logistic regression. The odds ratio in this analysis was

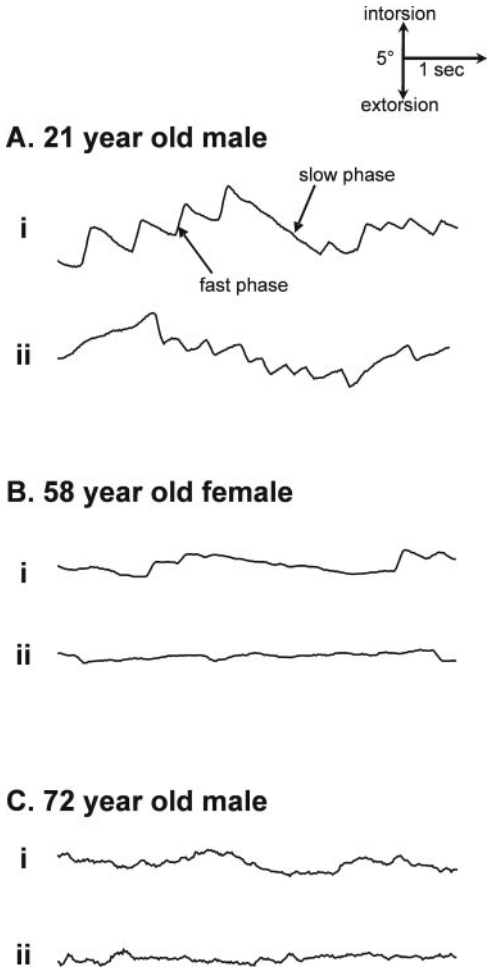


FIGURE 2. Original eye movement recordings of a 21-year-old subject (**A**), a 58-year-old subject (**B**), and a 72-year-old subject (**C**) at 400°/s stimulation. A downward slope indicated the eye making a slow phase in the extorsion direction, and an upward slope indicated an eye movement in the intorsion direction. tOKN was clearly seen in the 21-year-old man but was less obvious in the 58-year-old woman. Although some fluctuations in torsion were also seen in the 72-year-old man, tOKN was not apparent. Original data were smoothed using a five-point boxcar filter.

used to estimate the risk of being a nonresponder with age. The correlation between MSPV and age in subjects with measurable responses was also analyzed using the simple linear regression (Pearson product-moment correlation coefficient).

RESULTS

Examples of original eye movement recordings are displayed in Figure 2 showing monocular eye movement recordings from a 21-year-old subject (Fig. 2A), a 58-year-old subject (Fig. 2B), and a 72-year-old subject (Fig. 2C) at 400°/s stimulation in both rotational directions. The 21-year-old subject showed a clear tOKN response with slow phase in extorsion (Fig. 2Ai) and intorsion, (Fig. 2Aii), directions displaying no real difference in response. The 58-year-old subject showed a diminished tOKN response in both rotation directions (Fig. 2B). tOKN response was absent in the 72-year-old subject (Fig. 2C).

Figure 3 shows the correlation between age and MSPV in the intorsion and extorsion directions of all subjects at stimulus velocities of 40°/s (Fig. 3A) and 400°/s (Fig. 3B). The number of nonresponders (open circles for extorsion and crosses for intorsion) clearly increases with age. Consequently, logistic regression showed a significant change with age for stimulus rotations of 40°/s ($P = 0.0029$ [odds ratio, 0.91; 95% CI, 0.86–0.97] and $P = 0.0023$ [odds ratio, 0.90; 95% CI, 0.84–0.96] for extorsion and intorsion, respectively) and 400°/s ($P = 0.0026$ [odds ratio, 0.90; 95% CI, 0.84–0.96] and $P = 0.108$ [odds ratio, 0.76; 95% CI, 0.61–0.93] for extorsion and intorsion, respectively). For every 1-year increase in age, the risks were 9% and 10% of not responding to tOKN stimuli at 40°/s and 10.3% and 24.3% of not responding to tOKN stimuli at 400°/s in extorsion and intorsion directions, respectively. Within the age brackets of 19 to 40 years ($n = 10$; median age, 30; range, 19–36), 41 to 65 years ($n = 10$; median age, 52; range, 44–65), and older than 65 years ($n = 10$; median age, 68, range, 66–72), the number of responders (i.e., subjects who showed at least one response to stimuli in any direction of rotation at either stimulus velocity) were 10 of 10, 6 of 10, and 1 of 10, respectively.

Simple linear regression was used to investigate change in mean slow-phase velocity with age in subjects who displayed a measurable response (i.e., excluding zero values). Results of this analysis were not significant for either the 40°/s (extorsion: $r = 0.16$, $P = 0.6$; intorsion, $r = -0.050$, $P = 0.88$) or the 400°/s (extorsion: $r = -0.33$, $P = 0.23$; intorsion: $r = 0.34$, $P = 0.22$) stimulation.

Of the four older subjects (aged 56, 59, 63, and 72 years) tested at further stimulus velocities of 20°/s, 100°/s, 200°/s, 800°/s, and 1000°/s, the subjects aged 63 and 72 years demonstrated no detectable response when eye movement traces were analyzed across all stimulus velocities. The 56-year-old subject responded only at the stimulus velocity of 20°/s, in the counterclockwise direction, with an MSPV of 0.88°/s, and the 59-year-old subject responded at stimulus velocities of 200°/s in the clockwise direction and 20°/s in the counterclockwise direction, with MSPVs of 1.04°/s and 0.7°/s, respectively.

DISCUSSION

This study shows for the first time that tOKN is affected by aging. This effect was consistent over two stimulus velocities and occurred at approximately the same rate in extorsion or intorsion directions.

In a prospective cross-sectional study (249 subjects; age range, 18 days-89 years), horizontal OKN mean gain has been shown to undergo a small but significant decline after age 50.[2] This is in agreement with other studies comparing younger subjects with older subjects; superior horizontal OKN gains were always observed in the younger subjects.[3–5] Similarly, vertical OKN was also reduced in healthy elderly subjects (mean age, 70 ± 8 years), who had lower tracking gain and greater phase lag than healthy young subjects (mean age, 30 ± 6 years).[7]

The contrasting feature between our results and previous studies on horizontal and vertical OKN, however, is that the tOKN response was virtually undetectable in elderly subjects (older than 65 years; median age, 68), with only 1 in 10 demonstrating a response. The lack of response in the older subjects was also consistent when other stimulus velocities were used to assess the tOKN response in four subjects who originally did not respond to stimuli rotating at 40°/s or 400°/s. The older subjects, aged 63 and 72 years, did not show any response to other stimulus velocities, whereas the two younger subjects, aged 56 and 59, showed minimal response to stimuli rotating at 20°/s and 200°/s. Although previous studies showed reduced horizontal and vertical OKN gain in the elderly, a response was still evident.

Possible explanations for this could be that tOKN response has a very small gain (eye velocity in relation to stimulus

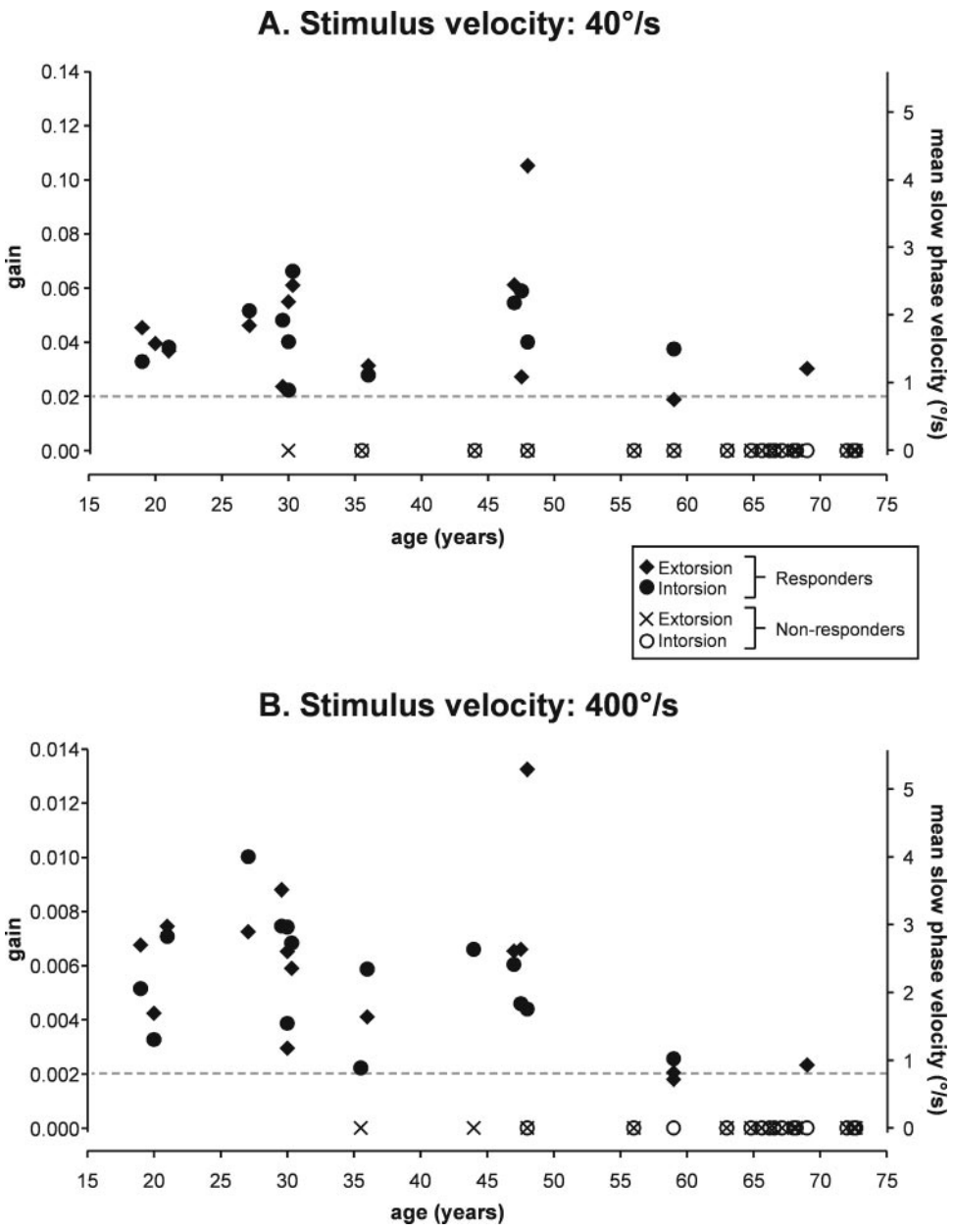


FIGURE 3. Scatterplots of mean slow-phase velocity in °/s compared with age in years at (**A**) 40°/s and (**B**) 400°/s stimulation. *Legend*: responders and nonresponders are distinguished. *Gray dotted line*: estimate of the level at which tOKN can be detected.

velocity), with stimuli up to 200°/s yielding a maximum response of approximately 3°/s.[1] Stimulus velocities of 40°/s and 400°/s were considered suitable for use because these had previously elicited a good response that was easily differentiated from the normally occurring noise in the recording.[1] However, it is possible that tOKN responses are closer to threshold than horizontal and vertical OKN responses, making them more sensitive to aging. Another possibility is that tOKN responses are present in the elderly but fall below the level of system noise. In general, VOG yields larger signal-to-noise ratios than torsion for horizontal and vertical eye movement recordings.

The tOKN response is essentially involuntary and not influenced by voluntary pursuit mechanisms. In general, we have limited capacity to make voluntary torsional eye movements in the primary position, though one early previous report by Balliet and Nakayama[11] in 1974 suggests that, with training, torsional pursuit can be generated voluntarily. The torsional "pursuit" they describe, however, does not involve the classic pursuit mechanism of tracking a single object of interest. Rather, it is driven by the alignment of static stimuli spanning the visual field. It is possible that tOKN is more prone to deterioration with age than horizontal and vertical OKN because pursuit cannot contribute to its generation.

Although the pursuit mechanism has been shown to decrease with age along the horizontal and vertical meridians,[3,7,12] recent findings from a longitudinal study in healthy elderly persons (older than 75 years)[13] describes horizontal smooth pursuit gains at two different velocities as not greatly affected by aging. In comparison, horizontal OKN measures showed a gradual significant age-related decline over a 9-year follow-up period. It is possible that the rates of horizontal and vertical OKN decline could be slowed by contribution of the pursuit system; tOKN shows a sharper decline.

The importance of higher cortical pathways compared with subcortical (retinogeniculate) pathways used for motion detection have been investigated.[6] Subjective measures of motion perception and objective measures of horizontal motion detection when viewing a random dot display were investigated in subjects from 19 to 92 years of age. Interestingly, the authors

found an age-related linear decrease in objective OKN responses and a subjective increase in the motion perception thresholds; however, they did not find an association between the two factors, suggesting that aging affects the neural mechanisms behind motion perception and motion detection at different cortical and subcortical levels.

The effects of aging on torsional eye movements generated through vestibular stimulation have also been described. Jahn et al.[14] measured torsional eye movements with VOG during stimulation of the vestibular nerve through galvanic vestibular stimulation (GVS) in 57 healthy subjects aged 20 to 69 years. They found that the magnitude of induced static ocular torsion and torsional nystagmus increased from the fourth to the sixth decade but decreased in the seventh decade. Listing's plane, the axis of rotation that governs the torsional position of the eye at all gaze positions,[15] has also been examined with respect to age. It was found that torsional position was more variable in older subjects (i.e., Listing plane was thicker) than in younger subjects when the whole body was repositioned to different static roll-and-pitch positions.[16]

In conclusion, we have shown for the first time an age-related deterioration of the tOKN responses in healthy subjects between 19 and 72 years of age. The responses appeared to be virtually eliminated in subjects older than 65 years of age.

References

1. Farooq SJ, Proudlock FA, Gottlob I. Torsional optokinetic nystagmus: normal response characteristics. *Br J Ophthalmol*. 2004;88:796–802.
2. Valmaggia C, Rutsche A, Baumann A, et al. Age related change of optokinetic nystagmus in healthy subjects: a study from infancy to senescence. *Br J Ophthalmol*. 2004;88:1577–1581.
3. Simons B, Buttner U. The influence of age on optokinetic nystagmus. *Eur Arch Psychiatry Neurol Sci*. 1985;234:369–373.
4. Kato I, Ishikawa M, Nakamura T, et al. Quantitative assessment of influence of aging on optokinetic nystagmus. *Acta Otolaryngol Suppl*. 1994;511:99–103.
5. Spooner JW, Sakala SM, Baloh RW. Effect of aging on eye tracking. *Arch Neurol*. 1980;37:575–576.
6. Tran DB, Silverman SE, Zimmerman K, Feldon SE. Age-related deterioration of motion perception and detection. *Graefes Arch Clin Exp Ophthalmol*. 1998;236:269–273.
7. Demer JL. Effect of aging on vertical visual tracking and visual-vestibular interaction. *J Vestib Res*. 1994;4:355–370.
8. Bono F, Oliveri RL, Zappia M, Aguglia U, Puccio G, Quattrone A. Computerized analysis of eye movements as a function of age. *Arch Gerontol Geriatr*. 1996;22:261–269.
9. Knox PC, Davidson JH, Anderson D. Age-related changes in smooth pursuit initiation. *Exp Brain Res*. 2005;165:1–7.
10. Thilo KV, Probst T, Bronstein AM, Ito Y, Gresty MA. Torsional eye movements are facilitated during perception of self-motion. *Exp Brain Res*. 1999;126:495–500.
11. Balliet R, Nakayama K. Training of voluntary torsion. *Invest Ophthalmol Vis Sci*. 1978;17:303–314.
12. Huaman AG, Sharpe JA. Vertical saccades in senescence. *Invest Ophthalmol Vis Sci*. 1993;34:2588–2595.
13. Kerber KA, Ishiyama GP, Baloh RW. A longitudinal study of oculomotor function in normal older people. *Neurobiol Aging*. 2006;27:1346–1353.
14. Jahn K, Naessl A, Schneider E, Strupp M, Brandt T, Dieterich M. Inverse U-shaped curve for age dependency of torsional eye movement responses to galvanic vestibular stimulation. *Brain*. 2003;126:1579–1589.
15. Leigh RJ, Zee DS. The neurology of eye movements. In: *Contemporary Neurology Series: 70*. Oxford: Oxford University Press; 2006:13.
16. Furman JM, Schor RH. Orientation of Listing's plane during static tilt in young and older human subjects. *Vision Res*. 2003;43:67–76.

Torsional optokinetic nystagmus: normal response characteristics

S J Farooq, F A Proudlock and I Gottlob

Br. J. Ophthalmol. 2004;88;796-802
doi:10.1136/bjo.2003.028738

EXTENDED REPORT

Torsional optokinetic nystagmus: normal response characteristics

S J Farooq, F A Proudlock, I Gottlob

Br J Ophthalmol 2004;**88**:796–802. doi: 10.1136/bjo.2003.028738

See end of article for authors' affiliations

Correspondence to: Shegufta Farooq, Department of Ophthalmology, University of Leicester, Robert Kilpatrick Clinical Sciences Building, Leicester Royal Infirmary, PO Box 65, Leicester LE2 7LX, UK; sjf18@le.ac.uk

Accepted for publication 18 September 2003

Background/aims: Few studies have investigated normal response characteristics of torsional optokinetic nystagmus (tOKN). The authors have investigated the effect of stimulus velocity and central/peripheral stimulation on tOKN.

Methods: Torsional OKN was elicited using a sinusoidal grating rotating at velocities of 3°/s to 1000°/s in clockwise and anticlockwise directions. To investigate the effect of central stimulation, stimulus size was varied from 2.86° to 50.8°. An artificial scotoma placed over a 50.8° stimulus was varied from 2.86° to 43.2° to investigate peripheral stimulation. Eight subjects participated in each experiment and torsional eye movements were recorded using video-oculography. The mean slow phase velocity (MSPV) and gain were calculated.

Results: The maximum gain occurred in response to 8°/s stimulation. The MSPV increased up to a stimulus velocity of 200°/s achieving a maximum of 3°/s in both directions. MSPV was linearly correlated with the log of stimulus velocity. The smallest field size, rotating at 40°/s, evoked 10% of the gain elicited by the largest display. When the most peripheral stimulus was used, the gain was maintained at 50% of the gain evoked when the full display was used.

Conclusions: A wide range of stimulus velocities can elicit tOKN and peripheral field stimulation contributes significantly to its response.

Torsional optokinetic nystagmus (tOKN) is an ocular motor response occurring when looking at a rotating stimulus. Similar to the horizontal and vertical OKN response, it consists of a slow phase in the direction of the stimulus followed by a fast phase in the opposite direction. Brecher first described the response[1] when he observed the conjunctival blood vessels of a subject that viewed a rotating sectored disc through a telescope.

There are only a few reports in which the tOKN gain (eye velocity in relation to stimulus velocity) to various stimuli has been investigated. Torsional OKN is reported to have a low gain, with values sometimes less than 0.1,[2–6] compared to horizontal and vertical OKN, where gains can approach 1. There has been no directional preponderance demonstrated for tOKN, with no difference in the response with subjects viewing a target rotating in the clockwise or anticlockwise directions.[2 3] In all previous reports, there was a small range of stimulus velocities used, the largest range being from 10–80°/s.[5] Reported gain values were also variable across subjects.

The effects of central and peripheral stimulation on the tOKN response have been investigated in only one previous study, on four subjects.[7] Using a series of artificial central and peripheral masks to occlude various proportions of the stimulus, the authors reported that the tOKN response was dominated by central stimulation.

The absence of central vision in patients with central scotomas due to, for example, age related macular degeneration, has been shown not to significantly affect the horizontal OKN response.[8 9] It has also been demonstrated that a ''filling-in'' response occurs in these patients which allows the stimulus to elicit optokinetic nystagmus.[10] In contrast, in normal subjects, the horizontal OKN response is dramatically reduced by occlusion of the central retina.[11] It is of interest to observe, therefore, whether a similar response can occur when using artificial central scotomas to elicit tOKN, since no such response has been commented on previously.[7]

In the current study, we have used video-oculography to systematically investigate the relation between stimulus velocity and tOKN gain using a large range of stimulus velocities, with the aim of establishing the limit and optimum level of response. Secondly, we have examined the effects of central and peripheral stimulation on the tOKN response by varying the size of central and peripheral field.

SUBJECTS AND METHODS

Subjects

A total of 20 healthy subjects, aged 20–59 years, were examined (mean age 34.9 years, 15 women and five men). Eight subjects participated in each experiment. All subjects had normal corrected visual acuity of 6/6 or better in each eye, good stereopsis on the TNO stereotest (between 60 and 15 seconds of arc), and were free from any ophthalmological, otological, or neurological symptoms. All tests were performed without any refractive correction. Six subjects had mild myopia or myopic astigmatism but were able to see the stimuli clearly from a distance of 120 cm without correction. The study received local ethical approval and was performed with consent after explanation of the nature and possible consequences of the study. The study was performed in accordance with tenets of the Declaration of Helsinki.

Methods

Eye movements were measured three dimensionally using a video-oculography technique (VOG), at a sampling rate of 50 Hz (Strabs system, Sensomotoric Instruments GmbH, Teltow, Germany). This consisted of infrared video cameras fitted on to a face mask firmly attached to the head using a rubber strap. Pupil tracking is used to derive horizontal and vertical movements. A segment of the iris is tracked to give torsional eye movements. The system has a spatial resolution of 0.03°, 0.02°, and 0.1° and a linearity of plus or minus 3.8% full scale reading (FSR), plus or minus 3.2% FSR, and plus or minus 1.4% FSR for horizontal, vertical, and torsional eye

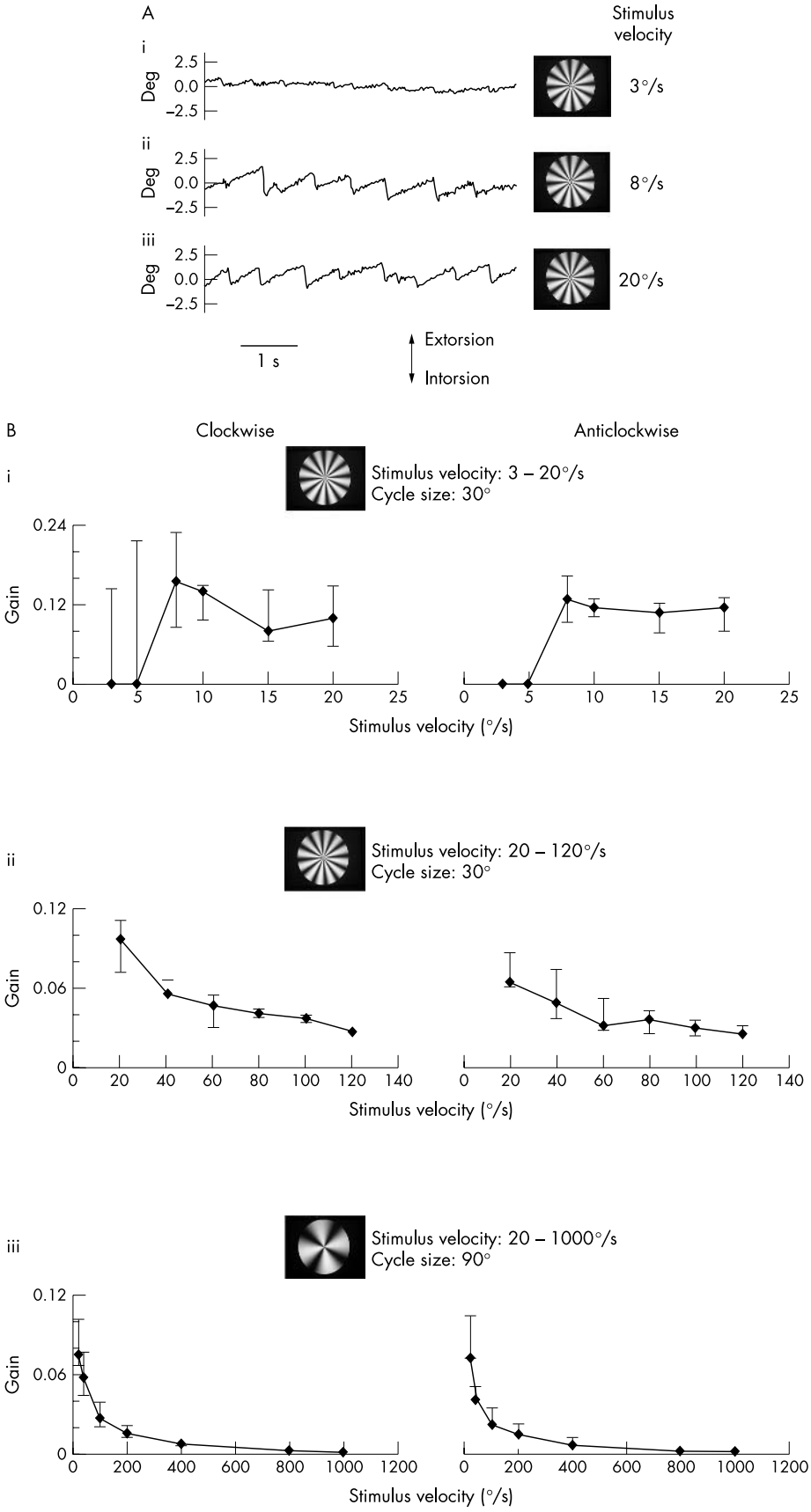


Figure 1 (A) Original recordings of the right eye from one representative subject showing the effect of stimulus velocity on torsional optokinetic nystagmus (tOKN). The stimulus is rotating in the clockwise direction. (B) Median torsional optokinetic nystagmus gain (plus or minus quartiles) of all subjects in response to stimuli rotating at: (i) 3–20°/s at a cycle size of 30°, (ii) 20–120°/s at a cycle size of 30°, and (iii) 20–1000°/s at a cycle size of 90°, in the clockwise and anticlockwise directions.

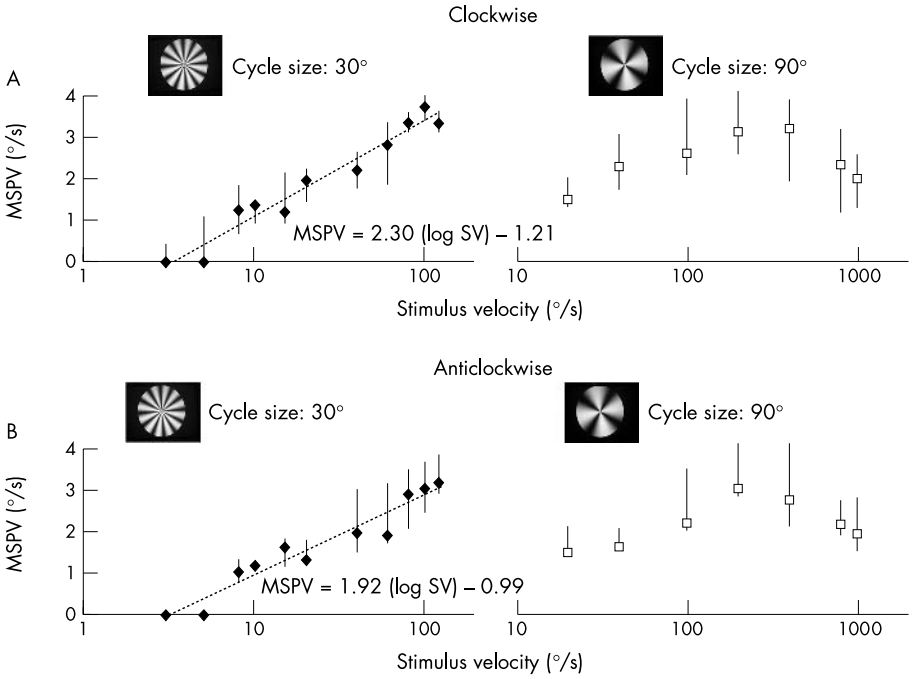


Figure 2 Mean slow phase velocity (median plus or minus quartiles) of all subjects in relation to the log of the stimulus velocity for stimulus velocities ranging from 3°/s to 120°/s at a cycle size of 30° (lefthand plots), and stimulus velocities ranging from 20°/s to 1000°/s at a cycle size of 90° (righthand plots), to clockwise and anticlockwise stimulation.

movements, respectively (company specifications). The range of linear measurement is plus or minus 25°, plus or minus 20°, and plus or minus 18° for horizontal, vertical, and torsional eye movements, respectively. The noise for the current experimental setup was estimated from the torsional recordings as 0.1–0.2° root mean squared (RMS) for torsional angle and 0.1–0.15°/s RMS for torsional velocity.

Each sample is an integration over a 20 ms period. The three dimensional VOG technique samples at a lower rate compared to the scleral search coil method (50 Hz compared to >250 Hz) and is not suitable for investigating fast phase parameters of nystagmus such as main sequence. However, the non-invasive nature of the VOG technique provides the advantage of allowing longer and more comfortable test periods to the subject.

The digitised ASCII file output for horizontal, vertical, and torsional data was converted into Spike 2 software files (Cambridge Electronic Design, UK) for subsequent analysis.

Every subject sat upright with their head stabilised on a chin rest placed 120 cm away from the stimulus. There were no head movements observed during testing in all subjects. The height of each subject was adjusted so that the subject's eyes and the centre of the stimulus were at the same level. The cameras of the VOG system were adjusted with the lights extinguished and the subject viewing a stationary stimulus similar to one that would be presented throughout testing. This method ensured that the pupil size, threshold, and contrast levels were similar to those under the experimental conditions. A five point calibration was performed with the subject fixating points positioned centrally, 15° in depression, right gaze, elevation and in left gaze. Torsional measurements are intrinsically calibrated since they are calculated from rotations of the iris. The software also performs a geometric compensation for distortions of the video image in oblique positions. The torsional angle was defined with reference to the initial image measured when setting up the recording.

The experimental stimulus was projected onto a rear projection screen of 1.75 m width and 1.17 metres height using an LCD projector (model Epson EMP 703, resolution 1024×768 pixels). The stimuli were generated using a visual stimulus generator (VSG 2/5, Cambridge Research Systems, Rochester, UK). The stimuli consisted of a rotating sinusoidal grating pattern of either a 30° or 90° cycle size subtending a maximum of 50.8 degrees in diameter (for example, see insets in fig 1B). The luminance of the grating pattern varied from 0.45 candelas/m^2 to 23 candelas/m^2 giving a luminance contrast of 96%. The stimulus was revolved around its central axis in both clockwise and anticlockwise directions to generate tOKN with variations in its velocity, cycle size and area of stimulation for different experimental conditions. All references to stimulus direction below are given from the perspective of the subject.

Experiment 1 was devised to measure the effect of stimulus velocity on the gain of tOKN. Stimulus velocities ranging from 3°/s to 1000°/s were used, the whole range of stimulus velocities was tested in three stages:

Stage 1: A sinusoidal grating pattern of cycle size 30° (inset in fig 1Bi), containing 12 radiating black and white sectors, was rotated at velocities of 3, 5, 8, 10, 15, and 20°/s applied in random order. Torsional OKN was recorded from subjects 1, 2, 3, 4, 5, 6, 7, and 8.

Stage 2: A sinusoidal grating pattern of cycle size 30° was rotated at velocities of 20, 40, 60, 80, 100, and 120°/s applied randomly and tOKN was recorded from subjects 1, 3, 9, 10, 11, 12, 13, and 14.

Stage 3: A sinusoidal grating pattern of cycle size 90° (inset in fig 1Biii), containing four black and white sectors, was rotated at 20, 40, 100, 200, 400, 800, and 1000°/s in random order, recording from subjects 1, 3, 15, 16, 17, 18, 19, and 20. The larger cycle size was used for faster angular velocities to limit counter-rotational stimulus projection effects and ensured good stimulus visibility by all subjects.

The subject was asked to fixate the centre of the stimulus binocularly and not to focus on any particular point of the stimulus. Each stimulus was presented for a period of 30 seconds followed by a blank phase of 15 seconds consisting of a black screen during which the subject was asked to continue to centrally fixate the stimulus.

Experiment 2 was designed to investigate the effect of central and peripheral stimulation on the gain of tOKN. To measure the effects of central stimulation, a sinusoidal grating pattern of cycle size 90° was projected at 2.86°, 6.2°,

12.4°, 24.9°, 35.1°, 43.2°, and 50.8° diameter (inset in fig 3A), in random order and tOKN was recorded from subjects 1, 2, 3, 4, 5, 6, 9, and 12. To assess varying degrees of peripheral stimulation on the tOKN response, an artificial central scotoma (black round spot) was incorporated into a sinusoidal grating pattern of cycle size 90° and diameter 50.8°. The occluder sizes were 2.86°, 6.2°, 12.4°, 24.9°, 35.1°, and 43.2° (inset in fig 4A) presented in random order and tOKN was recorded in the same subjects as in the central stimulation experiment. A response box was used by the subjects to indicate when they ''filled-in'' the missing central portion of the stimulus (Cambridge Research Systems, Rochester, UK). All tests consisted of a 30 second binocular stimulation period followed by a blank phase during which the subject was asked to stare straight ahead as in experiment 1. The horizontal and vertical eye position was monitored to ensure the subject was viewing the centre of the stimulus in both experiments. The effects of central and peripheral stimulation were measured at velocities of 40°/s and 400°/s.

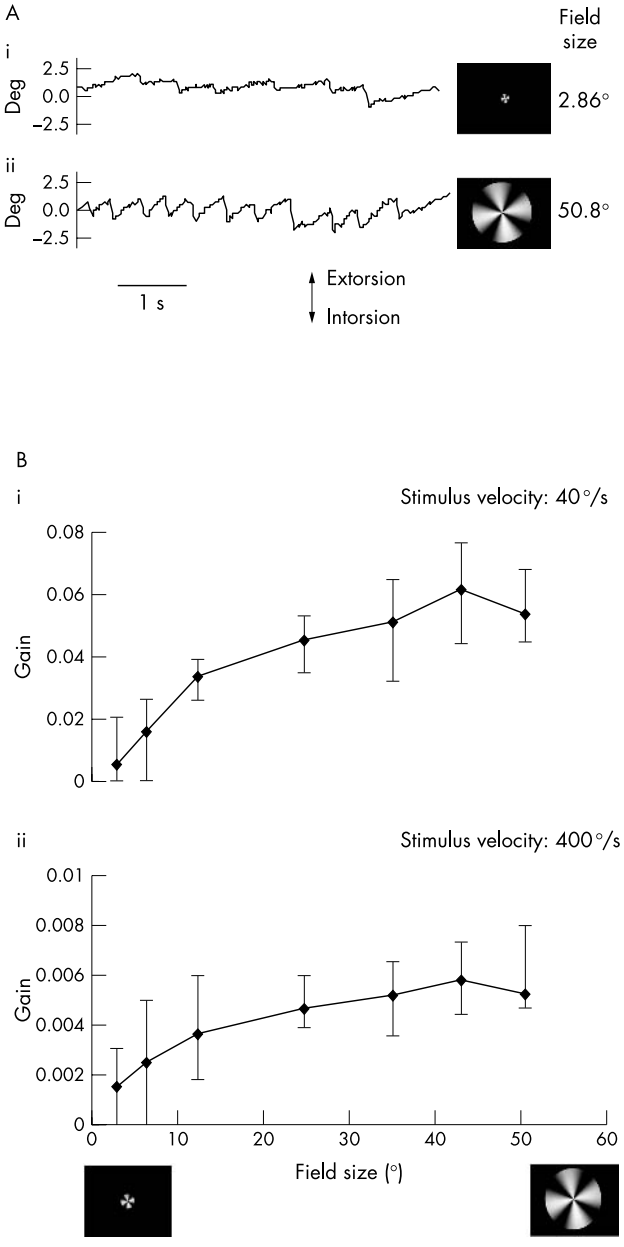


Figure 3 (A) Original recordings of the right eye in one representative subject showing the effect of increasing stimulus field size. The stimulus is rotating in the clockwise direction. (B) Median torsional optokinetic nystagmus gain (plus or minus quartiles) of all subjects in response to increasing stimulus field size with the stimulus rotating at 40°/s (i) and 400°/s (ii) in the clockwise direction.

Data analysis

The quality of the torsional eye movements depends on the visibility of the reference segment of the iris selected at the beginning of the trial and is given by the ''Strabs'' system for each torsional sample. Only data that exceeded torsional quality of 0.5 were used for analysis. Velocity traces of the torsional data were generated using a simple three point differentiator filter. A velocity threshold of 10°/s was used to determine saccades in the torsional recording. The mean velocity over a minimum of 10 slow phases from each 30 second trace was used to give the mean slow phase velocity (MSPV) for each stimulus. The gain value was then calculated by dividing this MSPV value by the stimulus velocity. Since the mean slow phase velocities and gains were not normally distributed across the subjects, medians and quartiles were used. For experiment 2, MSPV and gain values were calculated during periods of filling-in and during periods of no filling-in for three subjects.

RESULTS

Experiment 1: the effect of stimulus velocity on tOKN gain

Figure 1A shows original eye movement recordings obtained in one representative subject. Figures 1Ai, ii, and iii show original recordings obtained at 3°/s, 8°/s, and 20°/s, respectively. While there is a minimal tOKN response at 3°/s, a clear response is demonstrated at 8°/s and 20°/s. Only two out of eight subjects exhibited a visible tOKN response at 3°/s in the clockwise direction and one subject displayed a response in the anticlockwise direction.

Figure 1B shows median gains across all tested stimulus velocities. The largest gain occurred at 8°/s velocity in both clockwise and anticlockwise directions (fig 1Bi). Between the stimulus velocities 8°/s and 20°/s, the median gain remained fairly stable varying from 0.16 to 0.10 and 0.13 to 0.12 for clockwise and anticlockwise stimulation respectively. When stimulus velocity was increased from 20°/s to 120°/s, the median gain fell to 0.03 and 0.02 for clockwise and anticlockwise stimulation respectively (fig 1Bii). At stimulus velocities from 20°/s to 1000°/s the gain fell from 0.075 to 0.002 and 0.073 to 0.0019 for clockwise and anticlockwise stimulation (fig 1Biii). There was no difference in gain between the 30° and 90° cycle size stimuli, which were both tested at velocities of 20°/s, 40°/s, and 100°/s.

The MSPV increased as stimulus velocity increased up to 200°/s achieving a maximum MSPV of approximately 3°/s in both directions (fig 2). For a cycle size of 30° (see lefthand plots of fig 2), the response commenced at 3.4°/s stimulus velocity for clockwise stimulation and 3.3°/s stimulus velocity for anticlockwise stimulation (intercept with the x-axis). The MSPV was linearly correlated with the log of the stimulus velocity increasing by 2°/s per log unit up to the maximum stimulus velocity used of 120°/s ($r^2 = 0.95$ for clockwise stimuli and 0.93 for anticlockwise stimuli). For a cycle size of 90° (righthand plots of fig 2), the MSPV increased by approximately 1.5°/s per log unit increase from 20°/s to 200°/s. Above 200°/s, however, the MSPV began to tail off, decreasing to a MSPV of approximately 2°/s for the maximum stimulus velocity used of 1000°/s. For all velocities, there was no difference between clockwise and anticlockwise stimulation.

Experiment 2: the effect of stimulus area on tOKN gain

Figures 3Ai and ii show original recordings obtained using a stimulus size of 2.86° and 50.8° at 40°/s clockwise stimulation. The response to the 50.8° stimulus is much bigger than the response to the 2.86° stimulus. Figure 3Bi shows that the smallest field size of 2.86°, rotating at 40°/s evoked only 10% (0.0054) of the gain elicited by the largest field display (0.054) of 50.8°. Similarly, at 400°/s (fig 3Bii) the gain elicited by the smallest field size was 29% (0.0015) of the gain obtained by the largest stimulus (0.0052). Figure 4Ai and ii show original recordings obtained with the smallest (2.86°) and largest central occlusion (43.2°) showing the tOKN response to be present even when 85% of the stimulus was occluded (fig 4Aii). Figure 4Bi and ii illustrate the effect of increasing central occluder size on median tOKN gain at the two different stimulus velocities used. At 40°/s (fig 4Bi), when the largest central black spot occluded 85% (43.2°) of the 50.8° display, the gain was half (0.03) of the gain evoked when no central occluder was used (0.06). At 400°/s (fig 4Bii), using the largest central occluder, the gain was 17.5% (0.0014) of the gain evoked without any central occlusion (0.008).

During central occlusion experiments several subjects reported filling-in of the centrally occluded area by perceiving the continuation of the stripes of the stimulus into the occluded area. The perception of filling-in was changeable with some subjects constantly perceiving filling-in and others fluctuating between filling-in being present and absent within the 30 second period of stimulation.

Figure 5A shows a sample eye movement recording trace where filling-in and no filling-in are indicated during the same period of stimulation. There are no differences in waveform during the two conditions.

Three subjects were examined who showed both filling-in and non filling-in for the same stimulus to investigate whether this perception had any effect on the eye movements generated. The central occlusion experiments were repeated three times in the three subjects at a stimulus velocity of 40°/s. Figure 5B shows the tOKN gains during filling-in and none filling-in periods of peripheral stimulation in all three subjects. All subjects consistently demonstrated a filling-in response at the smaller sized central occluders of 2.86°, 6.2°, and 12.4°. There was no visible difference in tOKN gain during filling-in and non-filling-in periods.

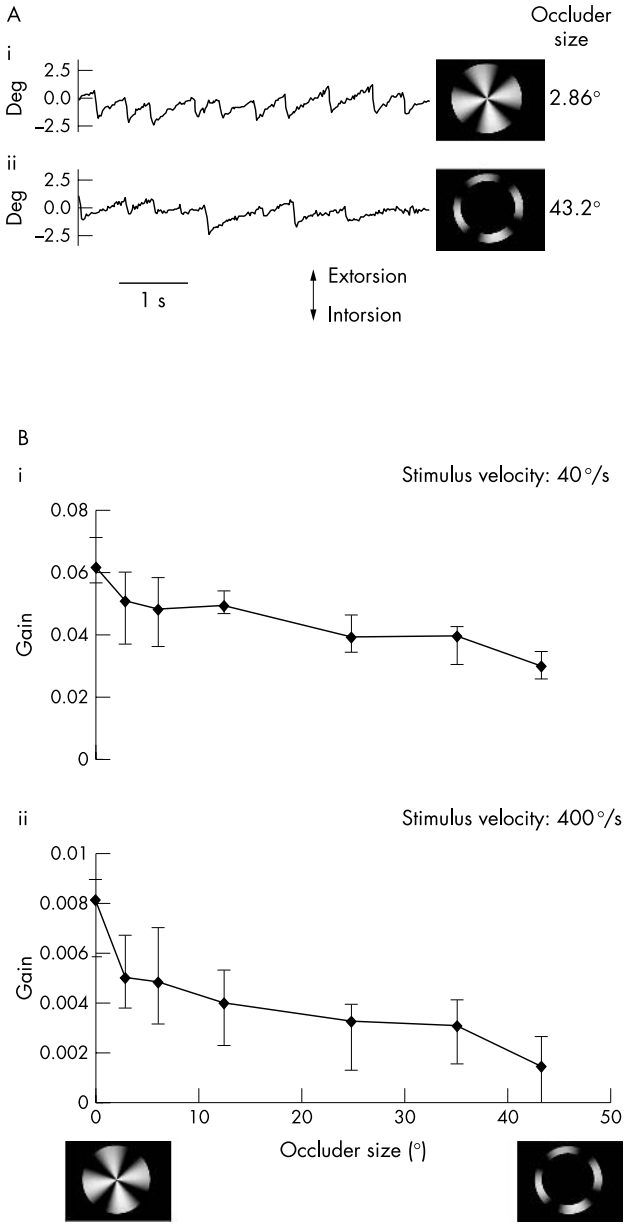


Figure 4 (A) Original recordings of right eye from one representative subject showing the effect of increasing central occluder size. The stimulus is rotating in the clockwise direction. (B) Median torsional optokinetic nystagmus gain (plus or minus quartiles) of all subjects in response to increasing central occluder size with the stimulus rotating at 40°/s (i) and 400°/s (ii) in the clockwise direction.

DISCUSSION

This study has shown, for the first time, that tOKN mean slow phase velocity (MSPV) is linearly related to the log of the stimulus velocity, with no difference in clockwise and anticlockwise stimulation. We have also shown that a significant proportion of the tOKN response is due to peripheral field stimulation, in contrast with a previous report, which states that the response is dependent mainly on central field stimulation.[7] When central areas of the stimulus were occluded subjects reported "filling-in" but this did not influence the tOKN response.

The maximum gain occurred in response to 8°/s stimulation with median values of 0.16 and 0.13 in clockwise and anticlockwise directions, respectively. Previously reported values[5 6] using similar stimulus velocities differ greatly. Collewijn *et al*.[6] reported a very low gain value of 0.035 to 6°/s tOKN stimulation in two subjects with highly variable results. In contrast, Morrow *et al*[5] reported a higher gain of 0.22 in response to 10°/s stimulation. This disparity may be due to differences in the stimuli used, since a random dot pattern was employed by Collewijn *et al*,[6] whereas radiating stripes, similar to that used in the present study, were used by Morrow *et al*.[5] In previous papers, studies employing a random pattern stimulus to elicit tOKN tend to show peak gain of less than 0.1,[2 3 6] whereas those using radiating stripes of various forms, with the exception of one study,[4] report peak gain responses of 0.1 or greater.[5 7 12]

Our results also demonstrate a measurable tOKN response at the higher range of stimulus velocities, with stimuli rotating as fast as 1000°/s achieving a gain of 0.002 and 0.0019 for clockwise and anticlockwise directions, respectively. It was also interesting to note that the MSPV increased as stimulus velocity increased up to 200°/s achieving a maximum MSPV of approximately 3°/s in both directions. Previous papers[2–6] have not used a large enough range of stimulus velocities to establish the peak response stimulus velocity. It is possible that the excessive linear velocities generated at the periphery of the faster rotating stimuli limit any further increase in the tOKN MSPV response.

There are two competing mechanisms involved in the generation of horizontal and vertical OKN. In humans, a pursuit mechanism is thought to dominate the OKN response, which has a rapid build up time and relies upon foveation. A delayed OKN system also contributes to human OKN, especially at higher stimulus velocities, but builds up more slowly and is generated by peripheral vision.[11 13] Accordingly, horizontal and vertical OKN gains approach 1 at lower stimulus velocities, but become low and irregular at stimulus velocities of 80–90°/s for horizontal OKN,[14] and 60°/s for vertical OKN.[13] Torsional OKN is not influenced by a pursuit mechanism since little or no target movement takes place at the fovea when the subject fixates on the target centre.[12] Consequently, torsional OKN, which is probably dominated by the peripheral field, exhibits low OKN gains at a wide range of stimulus velocities.

In our experiments, the smallest field size (2.86°) display evoked only a small proportion of the gain (10% at 40°/s) elicited by the largest field stimulus (50.8°). We have also demonstrated that when a large amount (85%) of the central field was occluded, a considerable amount of the tOKN gain was retained (50% at 40°/s). The only previous study[7] investigating the effects of central and peripheral stimulation on the tOKN response concluded that tOKN was preferentially stimulated using central stimuli. This was based on the assumption that when the central 75° of their display was occluded, only 30% of the full field tOKN response was maintained. In the central visual field, the rod free foveal region is approximately 1.25°.[15] Hence, occlusion of 75° also includes a significant amount of the peripheral field. The importance of the peripheral field for the tOKN response may be related to the degree of linear retinal slip, which increases with eccentricity for tOKN stimuli, in contrast with horizontal and vertical OKN stimuli. Greater retinal slip may also explain the more rapid drop-off in gain with increasing occluder size when using the faster stimulus velocity (400°/s). Linear velocities may become excessive at the periphery at this velocity causing a drop off in the tOKN response.

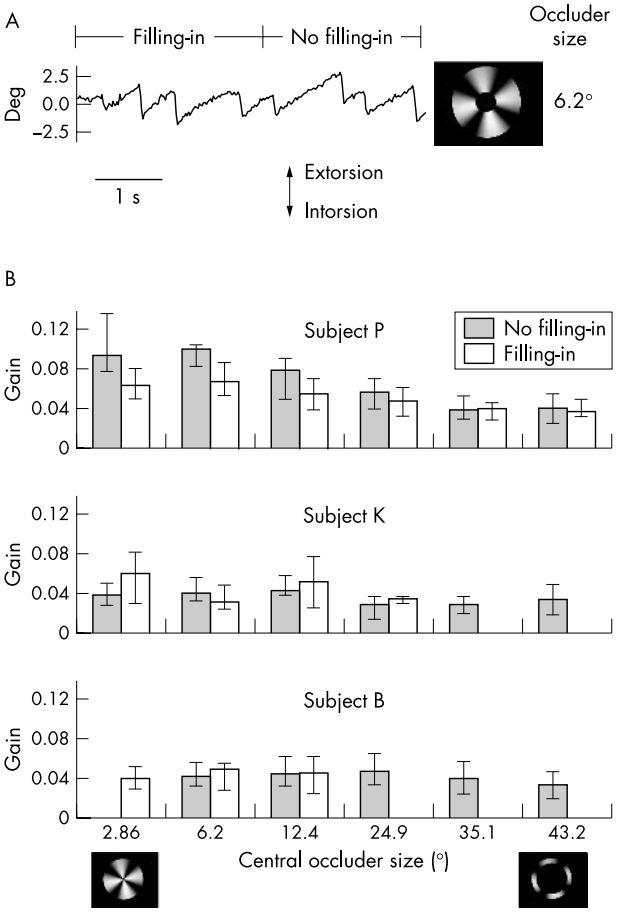


Figure 5 (A) Original recordings of right eye showing the effect of filling-in with the stimulus rotating in the clockwise direction at 40°/s. (B) Changes in torsional optokinetic nystagmus gain during periods of filling-in and no filling-in as central occluder increases in size with the stimulus rotating at 40°/s, in three subjects. Where only one bar is present, this indicates either filling-in or no filling-in for the whole period tested.

Subjects in our study perceive a completion of the peripheral stimulus into the centrally occluded area, which was more apparent when the smallest sized central occluders of 2.86°, 6.2°, and 12.4° were used. This process of ''filling-in'' causes visual stimuli to be perceived as arising from an area of the visual field where there is no actual visual input.[12] Filling-in of the peripheral stimulus did not have any measurable effects on the eye movements generated. This perception of filling-in has not been previously described for tOKN stimuli. However, Valmaggia *et al*[10] have described a filling-in response occurring during horizontal OKN in patients with central scotomas of 15°, 18°, and 16°. This filling-in elicited OKN whereas OKN was not present when there was no filling-in. The authors suggested that the ability of filling-in to directly effect eye movements is the result of motion sensitive areas of the visual cortex being stimulated through the active neural adaptation processes triggered during filling-in.[10]

In conclusion, we have demonstrated that a large range of stimulus velocities can elicit torsional optokinetic nystagmus, and that tOKN mean slow phase velocity is linearly related to the log of the stimulus velocity. We have also demonstrated that peripheral field stimulation provides a significant contribution of the tOKN response and that filling-in of torsional stimuli does not affect the eye movements generated.

Of further interest would be to study the effect of pathological central scotomas on tOKN and also conditions where it has been previously demonstrated that asymmetries of monocular horizontal and vertical OKN response are caused by impairment of early visual development—for example, congenital squint syndrome.[16 17]

ACKNOWLEDGEMENT

We thank the National Eye Research Centre (NERC).

Authors' affiliations
S J Farooq, F A Proudlock, I Gottlob, Department of Ophthalmology, University of Leicester, Robert Kilpatrick Clinical Sciences Building, Leicester Royal Infirmary, PO Box 65, Leicester LE2 7LX, UK

REFERENCES

1 **Brecher G**. Die optokinetische von Augenrollung and rotatorischem Nystagmus. *Pflugers Arch* 1934;**234**:13–28.
2 **Suzuki Y**, Shinmei Y, Nara H, *et al*. Effects of a fixation target on torsional optokinetic nystagmus. *Invest Ophthalmol Vis Sci* 2000;**41**:2954–9.
3 **Cheung BS**, Howard IP. Optokinetic torsion: dynamics and relation to circularvection. *Vis Res* 1991;**31**:1327–35.
4 **Seidman SH**, Leigh RJ, Thomas CW. Eye movements during motion after-effect. *Vis Res* 1992;**32**:167–71.
5 **Morrow MJ**, Sharpe JA. The effects of head and trunk position on torsional vestibular and optokinetic eye movements in humans. *Exp Brain Res* 1993;**95**:144–50.
6 **Collewijn H**, Van der Steen J, Ferman L, *et al*. Human ocular counterroll: assessment of static and dynamic properties from electromagnetic scleral coil recordings. *Exp Brain Res* 1985;**59**:185–96.
7 **Howard IP**, Sun L, Shen X. Cycloversion and cyclovergence: the effects of the area and position of the visual display. *Exp Brain Res* 1994;**100**:509–14.

8 **Valmaggia C**, Charlier J, Gottlob I. Optokinetic nystagmus in patients with central scotomas in age related macular degeneration. *Br J Ophthalmol* 2001;**85**:169–72.
9 **Abadi RV**, Pantazidou M. Monocular optokinetic nystagmus in humans with age-related maculopathy. *Br J Ophthalmol* 1997;**81**:123–9.
10 **Valmaggia C**, Gottlob I. Optokinetic nystagmus elicited by filling-in in adults with central scotoma. *Invest Ophthalmol Vis Sci* 2002;**43**:1804–8.
11 **Howard IP**, Ohmi M. The efficiency of the central and peripheral retina in driving optokinetic nystagmus. *Vision Res* 1984;**24**:969–76.
12 **Thilo KV**, Probst T, Bronstein AM, *et al*. Torsional eye movements are facilitated during perception of self-motion. *Exp Brain Res* 1999;**126**:495–500.
13 **Wei G**, Lafortune SH, Ireland DJ, *et al*. Stimulus velocity dependence of human vertical optokinetic nystagmus and afternystagmus. *J Vestib Res* 1992;**2**:99–106.
14 **Holm-Jensen S**, Peitersen E. The significance of the target frequency and the target speed in optokinetic nystagmus (OKN). *Acta Otolaryngol* 1979;**88**:110–16.
15 **Curcio CA**, Sloan KR, Kalina RE, *et al*. Human photoreceptor topography. *J Comp Neurol* 1990;**292**:497–523.
16 **Ramachandran VS.** In: Pessoa L, De Weerd P, eds. *Filling-in: from perceptual completion to cortical reorganisation*. New York: Oxford University Press, 2003:vii–xxii.
17 **Garbutt S**, Harris CM. A review of optokinetic nystagmus (OKN) in infants and children. *Br Orthopt J* 1999;**56**:1–10.

8. References

Abadi RV & Bjerre A. (2002). Motor and sensory characteristics of infantile nystagmus. *Br J Ophthalmol* **86,** 1152-1160.

Abadi RV, Dickinson C & Lomas M. (1982). Inverted and asymmetrical optokinetic nystagmus. In *Functional Basis of Ocular Motility Disorders*, ed. Lennerstrand G, Zee DS & Keller EL, pp. 143-146. Pergamon, Oxford.

Abadi RV & Dickinson CM. (1985). The influence of preexisting oscillations on the binocular optokinetic response. *Ann Neurol* **17,** 578-586.

Abadi RV & Dickinson CM. (1986). Waveform characteristics in congenital nystagmus. *Doc Ophthalmol* **64,** 153-167.

Abadi RV, Howard IP, Ohmi M, Howard T, Lee EE & Wright MJ. (1994). The rise time and steady-state gain of the human optokinetic response (OKR). *Invest Ophthalmol Vis Sci (Suppl)* **35,** 2035.

Abadi RV, Howard IP, Ohmi M & Lee EE. (2005). The effect of central and peripheral field stimulation on the rise time and gain of human optokinetic nystagmus. *Perception* **34,** 1015-1024.

Abadi RV & Pantazidou M. (1997). Monocular optokinetic nystagmus in humans with age-related maculopathy. *British Journal of Ophthalmology* **81,** 123-129.

Aiello A, Wright KW & Borchert M. (1994). Independence of optokinetic nystagmus asymmetry and binocularity in infantile esotropia. *Arch Ophthalmol* **112,** 1580-1583.

Angelaki DE & Hess BJ. (2005). Self-motion-induced eye movements: effects on visual acuity and navigation. *Nat Rev Neurosci* **6,** 966-976.

Ansons A, Davis H, Mein J & Trimble RB. (2000). Diagnosis and management of ocular motility disorders. 3rd ed. edn, pp. 475-487. Blackwell Science, Oxford.

Atkinson J. (1979). Development of optokinetic nystagmus in the human infant and monkey infant:an analogue to development in kittens In *Developmental neurobiology of vision*, ed. Freeman RD, pp. 277-287. Plenum Press [for] NATO Scientific Affairs Division, New York ; London.

Atkinson J & Braddick O. (1981). Development of optokinetic nystagmus in infants: an indicator of cortical binocularity? In *Eye movements : cognition and visual perception*, ed. Fisher DF, Monty RA & Senders JW, pp. 53-64. Lawrence Erlbaum, Hillsdale, N.J.

Averbuch-Heller L, Dell'Osso LF, Leigh RJ, Jacobs JB & Stahl JS. (2002). The torsional component of "horizontal" congenital nystagmus. *Journal of Neuro-Ophthalmology* **22,** 22-32.

Averbuch-Heller L, Rottach KG, Zivotofsky AZ, Suarez JI, Pettee AD, Remler BF & Leigh RJ. (1997). Torsional eye movements in patients with skew deviation and spasmodic torticollis: responses to static and dynamic head roll. *Neurology* **48,** 506-514.

Bahill AT & Stark L. (1975). Overlapping saccades and glissades are produced by fatigue in the saccadic eye movement system. *Exp Neurol* **48,** 95-106.

Bahill ATC, M.R, Stark, L. (1975). The main sequence, a tool for studying human eye movements. *Math Biosc* **24,** 191-204.

Bahn RS & Heufelder AE. (1993). Pathogenesis of Graves' ophthalmopathy. *N Engl J Med* **329,** 1468-1475.

Balliet R & Nakayama K. (1978). Training of voluntary torsion. *Invest Ophthalmol Vis Sci* **17,** 303-314.

Baloh RW, Enrietto J, Jacobson KM & Lin A. (2001). Age-related changes in vestibular function: a longitudinal study. *Ann N Y Acad Sci* **942,** 210-219.

Baloh RW, Jacobson KM & Socotch TM. (1993). The effect of aging on visual-vestibuloocular responses. *Exp Brain Res* **95,** 509-516.

Baloh RW, Richman L, Yee RD & Honrubia V. (1983). The dynamics of vertical eye movements in normal human subjects. *Aviat Space Environ Med* **54,** 32-38.

Baloh RW, Yee RD & Honrubia V. (1982). Clinical abnormalities of optokinetic nystagmus. In *Functional basis of ocular motility disorders : proceedings of a Wenner-Gren Center and Smith-Kettlewell Eye Research Foundation international symposium held in Wenner-Gren Center, Stockholm, 31 August-3 September 1981*, ed. Lennerstrand G, Zee DS & Keller EL, pp. 311-320. Pergamon, Oxford.

Baloh RW, Yee RD, Honrubia V & Jacobson K. (1988). A comparison of the dynamics of horizontal and vertical smooth pursuit in normal human subjects. *Aviat Space Environ Med* **59,** 121-124.

Barnes GR & Crombie JW. (1985). The interaction of conflicting retinal motion stimuli in oculomotor control. *Exp Brain Res* **59,** 548-558.

Barton JJ, Jama A & Sharpe JA. (1995). Saccadic duration and intrasaccadic fatigue in myasthenic and nonmyasthenic ocular palsies. *Neurology* **45,** 2065-2072.

Bense S, Janusch B, Vucurevic G, Bauermann T, Schlindwein P, Brandt T, Stoeter P & Dieterich M. (2006). Brainstem and cerebellar fMRI-activation during horizontal and vertical optokinetic stimulation. *Exp Brain Res* **174,** 312-323.

Bentley CR, Bronstein AM, Faldon M, Farmer S, Gresty MA, Matthews TD, Paine M, Plant GT & Riordan-Eva P. (1998). Fast eye movement initiation of ocular torsion in mesodiencephalic lesions. *Ann Neurol* **43,** 729-737.

Boghen D, Troost BT, Daroff RB, Dell'Osso LF & Birkett JE. (1974). Velocity characteristics of normal human saccades. *Invest Ophthalmol* **13,** 619-623.

Bohmer A & Baloh RW. (1990). Vertical optokinetic nystagmus and optokinetic afternystagmus in humans. *J Vestib Res* **1,** 309-315.

Bono F, Oliveri RL, Zappia M, Aguglia U, Puccio G & Quattrone A. (1996). Computerized analysis of eye movements as a function of age. *Arch Gerontol Geriatr* **22,** 261-269.

Brecher G. (1934). Die optokinetische von Augenrollung and rotatorischem Nystagmus. *Plugers Arch* **234,** 13-28.

British Orthoptic Society. (2001). Dictionary of comman terms in orthoptic practice. British Orthoptic society.

Brodsky MC & Tusa RJ. (2004). Latent nystagmus: vestibular nystagmus with a twist. *Arch Ophthalmol* **122,** 202-209.

Büttner-Ennever J & Buttner U. (1988). The reticular formation. In *Neuroanatomy of the oculomotor system*, ed. Büttner-Ennever JA, pp. 119-176. Elsevier, Amsterdam ; Oxford.

Buttner-Ennever JA & Buttner U. (1978). A cell group associated with vertical eye movements in the rostral mesencephalic reticular formation of the monkey. *Brain Res* **151,** 31-47.

Buttner U & Büttner-Ennever J. (2006). Present Concepts of Oculomotor Organization. In *Neuroanatomy of the oculomotor system*
Progress in brain research ; v 151, Updated extended ed. edn, ed. Büttner-Ennever JA, pp. 1-42. Elsevier, Amsterdam ; Oxford.

Buttner U, Buttner-Ennever JA & Henn V. (1977). Vertical eye movement related unit activity in the rostral mesencephalic reticular formation of the alert monkey. *Brain Res* **130,** 239-252.

Carl JR & Gellman RS. (1987). Human smooth pursuit: stimulus-dependent responses. *J Neurophysiol* **57,** 1446-1463.

Carpenter RHS. (1988). *Movements of the eyes*. Pion.

Cheung BS & Howard IP. (1991). Optokinetic torsion: dynamics and relation to circularvection. *Vision Research* **31,** 1327-1335.

Collewijn H, van der Mark F & Jansen TC. (1975). Precise recording of human eye movements. *Vision Res* **15,** 447-450.

Collewijn H, Van der Steen J, Ferman L & Jansen TC. (1985). Human ocular counterroll: assessment of static and dynamic properties from electromagnetic scleral coil recordings. *Experimental Brain Research* **59,** 185-196.

Crawford JD, Cadera W & Vilis T. (1991). Generation of torsional and vertical eye position signals by the interstitial nucleus of Cajal. *Science* **252,** 1551-1553.

Crawford JD & Vilis T. (1993). Modularity and parallel processing in the oculomotor integrator. *Exp Brain Res* **96,** 443-456.

Crone R & Everhard-Halm Y. (1976). Cyclofusion. In *Orthoptics : Past, Present, Future : 3rd International Orthoptic Congress : Papers*
ed. Moore S, Mein J & Stockbridge L, pp. 409-415. Grune and Stratton, New York.

Crone RA & Everhard-Hard Y. (1975). Optically induced eye torsion. I. Fusion cyclovergence. *Albrecht Von Graefes Arch Klin Exp Ophthalmol* **195,** 231-239.

Crossland WJ, Hu XJ & Rafols JA. (1994). Morphological study of the rostral interstitial nucleus of the medial longitudinal fasciculus in the monkey, Macaca mulatta, by Nissl, Golgi, and computer reconstruction and rotation methods. *J Comp Neurol* **347,** 47-63.

Das VE, Leigh RJ, Thomas CW, Averbuch-Heller L, Zivotofsky AZ, Discenna AO & Dell'Osso LF. (1995). Modulation of high-frequency vestibuloocular reflex during visual tracking in humans. *J Neurophysiol* **74,** 624-632.

Day S. (1995). Vision development in the monocular individual: implications for the mechanisms of normal binocular vision development and the treatment of infantile esotropia. *Trans Am Ophthalmol Soc* **93,** 523-581.

Dell'osso LF & Daroff RB. (1975). Congenital nystagmus waveforms and foveation strategy. *Doc Ophthalmol* **39,** 155-182.

Demer JL. (1994). Effect of aging on vertical visual tracking and visual-vestibular interaction. *J Vestib Res* **4,** 355-370.

Demer JL & Von Noorden GK. (1988). Optokinetic asymmetry in esotropia. *J Pediatr Ophthalmol Strabismus* **25,** 286-292.

Donders FC. (1848). Beiträge zur Lehre von den Bewegungen des menschlichen Auges. *Holländ Beitr Anat Physiol Wiss* **1,** 104-145.

Farooq SJ, Proudlock FA & Gottlob I. (2004). Torsional optokinetic nystagmus: normal response characteristics. *Br J Ophthalmol* **88,** 796-802.

Ferman L, Collewijn H & Van den Berg AV. (1987a). A direct test of Listing's law--I. Human ocular torsion measured in static tertiary positions. *Vision Res* **27,** 929-938.

Ferman L, Collewijn H & Van den Berg AV. (1987b). A direct test of Listing's law--II. Human ocular torsion measured under dynamic conditions. *Vision Res* **27,** 939-951.

Fletcher WA, Hain TC & Zee DS. (1990). Optokinetic nystagmus and afternystagmus in human beings: relationship to nonlinear processing of information about retinal slip. *Exp Brain Res* **81,** 46-52.

Fuchs AF, Mustari,M.J. (1993). The optokinetic response in primates and its possible neuronal substrate. In *Visual motion and its role in the stabilization of gaze*, ed. Miles FA & Wallman J, pp. 343-369. Elsevier, Amsterdam.

Fukushima K. (1987). The interstitial nucleus of Cajal and its role in the control of movements of head and eyes. *Prog Neurobiol* **29,** 107-192.

Fukushima K & Kaneko CR. (1995). Vestibular integrators in the oculomotor system. *Neurosci Res* **22,** 249-258.

Fukushima K, Kaneko CR & Fuchs AF. (1992). The neuronal substrate of integration in the oculomotor system. *Prog Neurobiol* **39,** 609-639.

Furman JM & Schor RH. (2003). Orientation of Listing's plane during static tilt in young and older human subjects. *Vision Res* **43,** 67-76.

Garbutt S, Han Y, Kumar AN, Harwood M, Harris CM & Leigh RJ. (2003a). Vertical optokinetic nystagmus and saccades in normal human subjects. *Invest Ophthalmol Vis Sci* **44,** 3833-3841.

Garbutt S, Han Y, Kumar AN, Harwood M, Rahman R & Leigh RJ. (2003b). Disorders of vertical optokinetic nystagmus in patients with ocular misalignment. *Vision Res* **43,** 347-357.

Garbutt S & Harris CM. (1999). A review of optokinetic nystagmus (OKN) in infants and children. *The British Orthoptic Journal* **56,** 1-10.

Gibson JJ. (1954). The visual perception of objective motion and subjective movement. *Psychol Rev* **61,** 304-314.

Gottlob I. (1997). Infantile nystagmus. Development documented by eye movement recordings. *Invest Ophthalmol Vis Sci* **38,** 767-773.

Groen E, Bos JE & de Graaf B. (1999). Contribution of the otoliths to the human torsional vestibulo-ocular reflex. *J Vestib Res* **9,** 27-36.

Grusser OJ. (1984). J.E. Purkyne's contributions to the physiology of the visual, the vestibular and the oculomotor systems. *Hum Neurobiol* **3,** 129-144.

Guyton DL. (1988). Ocular torsion: sensorimotor principles. *Graefes Archive for Clinical & Experimental Ophthalmology* **226,** 241-245.

Guyton DL. (2000). Dissociated vertical deviation: etiology, mechanism, and associated phenomena. Costenbader Lecture. *Journal of AAPOS: American Association for Pediatric Ophthalmology & Strabismus* **4,** 131-144.

Hainline L, Lemerise E, Abramov I & Turkel J. (1984). Orientational asymmetries in small-field optokinetic nystagmus in human infants. *Behav Brain Res* **13,** 217-230.

Halmagyi GM, Gresty MA & Leech J. (1980). Reversed optokinetic nystagmus (OKN): mechanism and clinical significance. *Ann Neurol* **7,** 429-435.

Harris C. (1997). Other eye movement disorders. In *Paediatric ophthalmology*, 2nd ed. edn, ed. Taylor D, pp. 897-924. Blackwell Science, Oxford ; Cambridge, Mass.

Harris CM, Jacobs M & Taylor D. (1994). The Development of bi-ocular and monocular optokinetic gain from 1-7 months. *invest Ophthalmol Vis Sci (Suppl)* **35,** 1829.

Harris CM, Kriss A, Shawkat F, Taylor D & Russell-Eggitt I. (1996). Delayed visual maturation in infants: a disorder of figure-ground separation? *Brain Res Bull* **40,** 365-369.

Haslwanter T. (1995). Mathematics of three-dimensional eye rotations. *Vision Res* **35,** 1727-1739.

Haustein W. (1992). Head-centric visual localization with lateral body tilt. *Vision Res* **32,** 669-673.

Haustein W & Mittelstaedt H. (1990). Evaluation of retinal orientation and gaze direction in the perception of the vertical. *Vision Res* **30,** 255-262.

Helmchen C, Rambold H & Buttner U. (1996). Saccade-related burst neurons with torsional and vertical on-directions in the interstitial nucleus of Cajal of the alert monkey. *Exp Brain Res* **112,** 63-78.

Helmchen C, Rambold H, Fuhry L & Buttner U. (1998). Deficits in vertical and torsional eye movements after uni- and bilateral muscimol inactivation of the interstitial nucleus of Cajal of the alert monkey. *Experimental Brain Research* **119,** 436-452.

Helmholtz Hv & Southall JPCb. *Helmholtz's treatise on physiological optics. Translated from the 3d German ed. Edited by James P. C. Southall*. New York, Dover Publications [1962].

Helmholtz Hv & Southall JPCb. (2000). Helmholtz's treatise on physiological optics. Reprinted from the 1924-5 edition edn, pp. 43. Thoemmes, Bristol.

Henson D. (1998). Visual Fields. pp. 2-3. Butterworth Heinmann, Oxford.

Hertle RW & Dell'Osso LF. (1999). Clinical and ocular motor analysis of congenital nystagmus in infancy.[comment]. *Journal of Aapos: American Association for Pediatric Ophthalmology & Strabismus* **3,** 70-79.

Hertle RW, Maldanado VK, Maybodi M & Yang D. (2002). Clinical and ocular motor analysis of the infantile nystagmus syndrome in the first 6 months of life. *Br J Ophthalmol* **86,** 670-675.

Hine T. (1985). The binocular contribution to monocular optokinetic nystagmus and after nystagmus asymmetries in humans. *Vision Res* **25,** 589-598.

Holm-Jensen S & Peitersen E. (1979). The significance of the target frequency and the target speed in optokinetic nystagmus (OKN). *Acta Otolaryngol* **88,** 110-116.

Honrubia V, Downey WL, Mitchell DP & Ward PH. (1968). Experimental studies on optokinetic nystagmus. II. Normal humans. *Acta Otolaryngol* **65,** 441-448.

Horn AK & Buttner-Ennever JA. (1998). Premotor neurons for vertical eye movements in the rostral mesencephalon of monkey and human: histologic identification by parvalbumin immunostaining. *J Comp Neurol* **392,** 413-427.

Horwood A. (2003). Neonatal ocular misalignments reflect vergence development but rarely become esotropia. *Br J Ophthalmol* **87,** 1146-1150.

Howard IP, Marton, C. (1997). Visual Pursuit over textured backgrounds in different depth planes. *Exp Brain Res* **90,** 625-629.

Howard IP & Ohmi M. (1984). The efficiency of the central and peripheral retina in driving human optokinetic nystagmus. *Vision Research* **24,** 969-976.

Howard IP & Rogers BJ. (2002). *Seeing in depth*. I. Porteous, Toronto.

Howard IP & Simpson WA. (1989). Human optokinetic nystagmus is linked to the stereoscopic system. *Experimental Brain Research* **78,** 309-314.

Howard IP, Sun L & Shen X. (1994). Cycloversion and cyclovergence: the effects of the area and position of the visual display. *Experimental Brain Research* **100,** 509-514.

Huaman AG & Sharpe JA. (1992). Vertical smooth pursuit in senescence. *Invest Ophthalmol Vis Sci* **33,** 1417.

Hutton SB & Tegally D. (2005). The effects of dividing attention on smooth pursuit eye tracking. *Exp Brain Res* **163,** 306-313.

Irving EL, Goltz HC, Steinbach MJ & Kraft SP. (1998). Vertical latent nystagmus component and vertical saccadic asymmetries in subjects with dissociated vertical deviation. *J Aapos* **2,** 344-350.

Jacobs M, Harris CM, Shawkat F & Taylor D. (1997). Smooth pursuit development in infants. *Aust N Z J Ophthalmol* **25,** 199-206.

Jahn K, Naessl A, Schneider E, Strupp M, Brandt T & Dieterich M. (2003). Inverse U-shaped curve for age dependency of torsional eye movement responses to galvanic vestibular stimulation. *Brain* **126,** 1579-1589.

Jampel R, Stearns A & Bugola J. (1976). Cyclophoria or cyclovergence: illusion or reality? In *Orthoptics : Past, Present, Future : 3rd International Orthoptic Congress : Papers*
ed. Moore S, Mein J & Stockbridge L, pp. 403-408. Grune and Stratton, New York.

Jung R & Kornhuber H. (1964). Results of electronystagmography in man: the value of optokinetic, vestibular and sponatanoeous nystagmus for neurological diagnosis and research. In *The oculomotor system*, ed. Bender MB, pp. 428-483. Harper & Row, New York.

Kato I, Ishikawa M, Nakamura T, Watanabe J, Harada K, Kanayama R, Aoyagi M & Koike Y. (1994). Quantitative assessment of influence of aging on optokinetic nystagmus. *Acta Otolaryngol Suppl* **511,** 99-103.

Kerber KA, Ishiyama GP & Baloh RW. (2006). A longitudinal study of oculomotor function in normal older people. *Neurobiol Aging* **27,** 1346-1353.

Kertesz AE & Jones RW. (1969). The effect of angular velocity of stimulus on human torsional eye movements. *Vision Res* **9,** 995-998.

Kertesz AE & Jones RW. (1970). Human cyclofusional response. *Vision Res* **10,** 891-896.

Kimmig H, Haussmann K, Mergner T & Lucking CH. (2002). What is pathological with gaze shift fragmentation in Parkinson's disease? *J Neurol* **249,** 683-692.

Kleinschmidt A, Thilo KV, Buchel C, Gresty MA, Bronstein AM & Frackowiak RS. (2002). Neural correlates of visual-motion perception as object- or self-motion. *Neuroimage* **16,** 873-882.

Knox PC, Davidson JH & Anderson D. (2005). Age-related changes in smooth pursuit initiation. *Exp Brain Res* **165,** 1-7.

Kommerell G & Mehdorn E. (1982). Is an optokinetic defect the cause of congenital and latent nystagmus. In *Functional Basis of Ocular Motility Disorders*, ed. Lennerstrand G, Zee DS & Keller EL, pp. 159-167. Pergamon, Oxford.

Kommerell G, Olivier D & Theopold H. (1976). Adaptive programming of phasic and tonic components in saccadic eye movements. Investigations of patients with abducens palsy. *Invest Ophthalmol* **15,** 657-660.

Lasker AG & Zee DS. (1997). Ocular motor abnormalities in Huntington's disease. *Vision Res* **37,** 3639-3645.

Lazenby C. (2000). Cyclofusion: a literature review. *British Orthoptic Journal* **57,** 50-53.

Leigh RJ & Zee DS. (2006). *The neurology of eye movements*. Oxford University Press, Oxford.

Lopez C, Borel L, Magnan J & Lacour M. (2005). Torsional optokinetic nystagmus after unilateral vestibular loss: asymmetry and compensation. *Brain* **128,** 1511-1524.

Lopez L, Bronstein AM, Gresty MA, Rudge P & du Boulay EP. (1992). Torsional nystagmus. A neuro-otological and MRI study of thirty-five cases. *Brain* **115,** 1107-1124.

Lopez LI, Gresty MA, Bronstein AM, du Boulay EP & Rudge P. (1995). Acquired pendular nystagmus: oculomotor and MRI findings. *Acta Otolaryngol Suppl* **520 Pt 2,** 285-287.

Macadar O & Budelli R. (1984). Mechanisms of sensory adaptation in the isolated utricle. *Exp Neurol* **86,** 147-159.

Maddox EE. (1893). *The clinical use of prisms and the decentering of lenses*. John Wright & Co., Bristol.

Manali S. (2006). Vestibuloocular Reflex Testing.

Matsuo V & Cohen B. (1984). Vertical optokinetic nystagmus and vestibular nystagmus in the monkey: up-down asymmetry and effects of gravity. *Exp Brain Res* **53,** 197-216.

McLean R, Proudlock F, Thomas S, Degg C & Gottlob I. (2007). Congenital nystagmus: randomized, controlled, double-masked trial of memantine/gabapentin. *Ann Neurol* **61,** 130-138.

Mein J & Harcourt B. (1986). *Diagnosis and management of ocular motility disorders*. Blackwell Scientific, Oxford.

Mesulam MM, Van Hoesen GW, Pandya DN & Geschwind N. (1977). Limbic and sensory connections of the inferior parietal lobule (area PG) in the rhesus monkey: a study with a new method for horseradish peroxidase histochemistry. *Brain Res* **136,** 393-414.

Meyer CH, Lasker AG & Robinson DA. (1985). The upper limit of human smooth pursuit velocity. *Vision Res* **25,** 561-563.

Mikaelian HH, Mikaelian DM & Cameron EL. (1990). Adaptation to tilt is not produced by eye-muscle potentiation. *Vision Res* **30,** 779-783.

Mohn G, Sireteanu R & van Hof-van Duin J. (1986). The relation of monocular optokinetic nystagmus to peripheral binocular interactions. *Invest Ophthalmol Vis Sci* **27,** 565-573.

Morrow MJ & Sharpe JA. (1993). The effects of head and trunk position on torsional vestibular and optokinetic eye movements in humans. *Experimental Brain Research* **95,** 144-150.

Moschovakis AK, Scudder CA & Highstein SM. (1991a). Structure of the primate oculomotor burst generator. I. Medium-lead burst neurons with upward on-directions. *J Neurophysiol* **65,** 203-217.

Moschovakis AK, Scudder CA & Highstein SM. (1996). The microscopic anatomy and physiology of the mammalian saccadic system. *Prog Neurobiol* **50,** 133-254.

Moschovakis AK, Scudder CA, Highstein SM & Warren JD. (1991b). Structure of the primate oculomotor burst generator. II. Medium-lead burst neurons with downward on-directions. *J Neurophysiol* **65,** 218-229.

Murasugi CM & Howard IP. (1989a). Up-down asymmetry in human vertical optokinetic nystagmus and afternystagmus: contributions of the central and peripheral retinae. *Exp Brain Res* **77,** 183-192.

Murasugi CM & Howard IP. (1989b). Up-down asymmetry in human vertical optokinetic nystagmus and afternystagmus: contributions of the central and peripheral retinae. *Experimental Brain Research* **77,** 183-192.

Mustari MJ, Tusa RJ, Burrows AF, Fuchs AF & Livingston CA. (2001). Gaze-stabilizing deficits and latent nystagmus in monkeys with early-onset visual deprivation: role of the pretectal not. *J Neurophysiol* **86,** 662-675.

Naegele JR & Held R. (1982). The postnatal development of monocular optokinetic nystagmus in infants. *Vision Res* **22,** 341-346.

Neville BG, Lake BD, Stephens R & Sanders MD. (1973). A neurovisceral storage disease with vertical supranuclear ophthalmoplegia, and its relationship to Niemann-Pick disease. A report of nine patients. *Brain* **96,** 97-120.

Newsome WT & Pare EB. (1988). A selective impairment of motion perception following lesions of the middle temporal visual area (MT). *J Neurosci* **8,** 2201-2211.

Ogino S, Kato I, Sakuma A, Takahashi K & Takeyama I. (1996). Vertical optokinetic nystagmus in normal individuals. *Acta Otolaryngol Suppl* **522,** 38-42.

Oohira A, Goto K & Ozawa T. (1986). Hypermetric saccades and adaptive response. *Neuroophthlamology* **3,** 353-356.

Paige GD. (1992). Senescence of human visual-vestibular interactions. 1. Vestibulo-ocular reflex and adaptive plasticity with aging. *J Vestib Res* **2,** 133-151.

Paige GD. (1994). Senescence of human visual-vestibular interactions: smooth pursuit, optokinetic, and vestibular control of eye movements with aging. *Exp Brain Res* **98,** 355-372.

Pansell T, Tribukait A, Bolzani R, Schworm HD & Ygge J. (2005a). Drift in ocular counterrolling during static head tilt. *Ann N Y Acad Sci* **1039,** 554-557.

Pansell T, Tribukait A, Bolzani R, Schworm HD & Ygge J. (2005b). Drift in ocular torsion during sustained head tilt. *Strabismus* **13,** 115-121.

Pasik P, Pasik T, Valciukas JA & Bender MB. (1971). Vertical optokinetic nystagmus in the split-brain monkey. *Exp Neurol* **30,** 162-171.

Peterka RJ, Black FO & Schoenhoff MB. (1990a). Age-related changes in human vestibulo-ocular and optokinetic reflexes: pseudorandom rotation tests. *J Vestib Res* **1,** 61-71.

Peterka RJ, Black FO & Schoenhoff MB. (1990b). Age-related changes in human vestibulo-ocular reflexes: sinusoidal rotation and caloric tests. *J Vestib Res* **1,** 49-59.

Petrov AP & Zenkin GM. (1973). Torsional eye movements and constancy of the visual field. *Vision Res* **13,** 2465-2477.

Poljac E, Lankheet MJ & van den Berg AV. (2005). Perceptual compensation for eye torsion. *Vision Res* **45,** 485-496.

Purkinje J. (1823). *Beobachtungen und Versuche zur Physiologie der Sinne.* Prague.

Qing Y & Kapoula Z. (2004). Saccade-vergence dynamics and interaction in children and in adults. *Exp Brain Res* **156,** 212-223.

Rambold H, Neumann G, Sander T & Helmchen C. (2006). Age-related changes of vergence under natural viewing conditions. *Neurobiol Aging* **27,** 163-172.

Rashbass C. (1961). The relationship between saccadic and smooth tracking eye movements. *J Physiol* **159,** 326-338.

Repka MX, Claro MC, Loupe DN & Reich SG. (1996). Ocular motility in Parkinson's disease. *J Pediatr Ophthalmol Strabismus* **33,** 144-147.

Robinson DA. (1963). A Method of Measuring Eye Movement Using a Scleral Search Coil in a Magnetic Field. *IEEE Trans Biomed Eng* **10,** 137-145.

Robinson DA. (1965). The mechanics of human smooth pursuit eye movement. *J Physiol* **180,** 569-591.

Rottach KG, Zivotofsky AZ, Das VE, Averbuch-Heller L, Discenna AO, Poonyathalang A & Leigh RJ. (1996). Comparison of horizontal, vertical and diagonal smooth pursuit eye movements in normal human subjects. *Vision Res* **36,** 2189-2195.

Roy MS, LaChapelle P & Lepore F. (1989). Maturation of the optokinetic reflex as a function of the speed of stimulation in full term and preterm infants *Clin Vis Sci* **4,** 357-366.

Safran AB & Landis T. (1999). From cortical plasticity to unawareness of visual field defects. *J Neuroophthalmol* **19,** 84-88.

Saito H, Yukie M, Tanaka K, Hikosaka K, Fukada Y & Iwai E. (1986). Integration of direction signals of image motion in the superior temporal sulcus of the macaque monkey. *J Neurosci* **6,** 145-157.

Sakaguchi M, Taguchi K, Sato K, Akahira T, Netsu K, Katsuno S & Ishiyama T. (1997). Vestibulo-ocular reflex and visual vestibulo-ocular reflex during sinusoidal rotation in children. *Acta Otolaryngol Suppl* **528,** 70-73.

Schiff D, Cohen B & Raphan T. (1986). Roll OKN and OKAN: effects of head position on velocity storage in the monkey. *Soc Neurosci Abstr* **12,** 774.

Schor CM, Fusaro RE, Wilson N & McKee SP. (1997). Prediction of early-onset esotropia from components of the infantile squint syndrome. *Investigative Ophthalmology & Visual Science* **38,** 719-740.

Schor CM & Levi DM. (1980). Disturbances of small-field horizontal and vertical optokinetic nystagmus in amblyopia. *Invest Ophthalmol Vis Sci* **19,** 668-683.

Seidman SH, Leigh RJ & Thomas CW. (1992). Eye movements during motion after-effect. *Vision Research* **32,** 167-171.

Semmlow JL, Hung GK & Ciuffreda KJ. (1986). Quantitative assessment of disparity vergence components. *Invest Ophthalmol Vis Sci* **27,** 558-564.

Shawkat FS, Harris CM, Taylor DS, Thompson DA, Russell-Eggitt I & Kriss A. (1995). The optokinetic response differences between congenital profound and nonprofound unilateral visual deprivation. *Ophthalmology* **102,** 1615-1622.

Simons B & Buttner U. (1985). The influence of age on optokinetic nystagmus. *Eur Arch Psychiatry Neurol Sci* **234,** 369-373.

Spooner JW, Sakala SM & Baloh RW. (1980). Effect of aging on eye tracking. *Arch Neurol* **37,** 575-576.

Straumann D, Zee DS, Solomon D & Kramer PD. (1996). Validity of Listing's law during fixations, saccades, smooth pursuit eye movements, and blinks. *Exp Brain Res* **112,** 135-146.

Sullivan MJ & Kertesz AE. (1979). Peripheral stimulation and human cyclofusional response. *Invest Ophthalmol Vis Sci* **18,** 1287-1291.

Suzuki Y, Buttner-Ennever JA, Straumann D, Hepp K, Hess BJ & Henn V. (1995). Deficits in torsional and vertical rapid eye movements and shift of Listing's plane after uni- and bilateral lesions of the rostral interstitial nucleus of the medial longitudinal fasciculus. *Exp Brain Res* **106,** 215-232.

Suzuki Y, Shinmei Y, Nara H & Ifukube T. (2000). Effects of a fixation target on torsional optokinetic nystagmus. *Investigative Ophthalmology & Visual Science* **41,** 2954-2959.

Tanaka K & Saito H. (1989). Analysis of motion of the visual field by direction, expansion/contraction, and rotation cells clustered in the dorsal part of the medial superior temporal area of the macaque monkey. *J Neurophysiol* **62,** 626-641.

Tarpey P, Thomas S, Sarvananthan N, Mallya U, Lisgo S, Talbot CJ, Roberts EO, Awan M, Surendran M, McLean RJ, Reinecke RD, Langmann A, Lindner S, Koch M, Jain S, Woodruff G, Gale RP, Degg C, Droutsas K, Asproudis I, Zubcov AA, Pieh C, Veal CD, Machado RD, Backhouse OC, Baumber L, Constantinescu CS, Brodsky MC, Hunter DG, Hertle RW, Read RJ, Edkins S, O'Meara S, Parker A, Stevens C, Teague J, Wooster R, Futreal PA, Trembath RC, Stratton MR, Raymond FL & Gottlob I. (2006). Mutations in FRMD7, a newly identified member of the FERM family, cause X-linked idiopathic congenital nystagmus. *Nat Genet* **38,** 1242-1244.

Ter Braak J. (1936). Untersuchengen uber optokinetischen nystagmus. *Arch Neerl Physiol* **21,** 309-376.

Thilo KV, Probst T, Bronstein AM, Ito Y & Gresty MA. (1999). Torsional eye movements are facilitated during perception of self-motion. *Experimental Brain Research* **126,** 495-500.

Thomas S, Frank A, Sarvananthan N, RobertsEryl., Awan M, ., McLean R, Surendran M, A SAK, Shegufta JF, Chris D, Richard PG, Robert DR, Geoffrey W, Andrea L, Susanne L, Sunila J, Patrick T, Lucy R & Irene G. (2008). Phenotypical Characteristics of Idiopathic Infantile Nystagmus with and without Mutations in FRMD7
In press.

Tran DB, Silverman SE, Zimmerman K & Feldon SE. (1998). Age-related deterioration of motion perception and detection. *Graefes Arch Clin Exp Ophthalmol* **236,** 269-273.

Tribukait A. (2003). Human vestibular memory studied via measurement of the subjective horizontal during gondola centrigugen. *Neuro Biol Learn Mem* **80,** 1-10.

Troost BT, Daroff RB, Weber RB & Dell'Osso LF. (1972). Hemispheric control of eye movements. II. Quantitative analysis of smooth pursuit in a hemispherectomy patient. *Arch Neurol* **27,** 449-452.

Tusa RJ, Mustari MJ, Burrows AF & Fuchs AF. (2001). Gaze-stabilizing deficits and latent nystagmus in monkeys with brief, early-onset visual deprivation: eye movement recordings. *J Neurophysiol* **86,** 651-661.

Tusa RJ, Mustari MJ, Das VE & Boothe RG. (2002). Animal models for visual deprivation-induced strabismus and nystagmus. *Ann N Y Acad Sci* **956,** 346-360.

Tychsen L & Lisberger SG. (1986). Visual motion processing for the initiation of smooth-pursuit eye movements in humans. *J Neurophysiol* **56,** 953-968.

Tychsen L, R. HR & J.A. T. (1984). Defective downward smooth pursuit in infantile strabismus. *Invest Ophthalmol Vis Sci (Suppl)* **25,** 74.

Valmaggia C, Charlier J & Gottlob I. (2001). Optokinetic nystagmus in patients with central scotomas in age related macular degeneration. *British Journal of Ophthalmology* **85,** 169-172.

Valmaggia C & Gottlob I. (2002). Optokinetic nystagmus elicited by filling-in in adults with central scotoma. *Investigative Ophthalmology & Visual Science* **43,** 1804-1808.

Valmaggia C, Proudlock F & Gottlob I. (2003). Optokinetic nystagmus in strabismus: are asymmetries related to binocularity? *Invest Ophthalmol Vis Sci* **44,** 5142-5150.

Valmaggia C, Rutsche A, Baumann A, Pieh C, Bellaiche Shavit Y, Proudlock F & Gottlob I. (2004). Age related change of optokinetic nystagmus in healthy subjects: a study from infancy to senescence. *Br J Ophthalmol* **88,** 1577-1581.

van den Berg AV & Collewijn H. (1986). Human smooth pursuit: effects of stimulus extent and of spatial and temporal constraints of the pursuit trajectory. *Vision Res* **26,** 1209-1222.

van den Berg AV & Collewijn H. (1988). Directional asymmetries of human optokinetic nystagmus. *Exp Brain Res* **70,** 597-604.

van Hof-van Duin J & Mohn G. (1986). Monocular and binocular optokinetic nystagmus in humans with defective stereopsis. *Invest Ophthalmol Vis Sci* **27,** 574-583.

Van Rijn L, Simonsz H & ten Tusscher M. (1997). Disssociated vertical deviation and eye torsion: relation to disparity induced vertical vergence *Strabismus* **5,** 13-20.

Vivian AJ, Harris CM & Kriss A. (1993). Oculomotor signs in infantile Gaucher disease. *Neuro-ophthalmology* **13,** 151-155.

Von Noorden GK. (1977). Mechanisms of amblyopia. *Doc Ophthalmol* **34,** 93.

Von Noorden GK. (1990a). *Binocular vision and ocular motility : theory and management of strabismus*. C. V. Mosby, St.Louis, Mo.

Von Noorden GK. (1990b). Binocular vision and ocular motility : theory and management of strabismus. 4th ed. edn, pp. 200. Mosby, St. Louis.

Von Noorden GK & Campos EC. (2001). *Binocular vision and ocular motility : theory and management of strabismus*. Mosby, St. Louis, Mo. ; London.

Washio N, Suzuki Y, Sawa M & Ohtsuka K. (2005). Gain of human torsional optokinetic nystagmus depends on horizontal disparity. *Invest Ophthalmol Vis Sci* **46,** 133-136.

Wei G, Lafortune SH, Ireland DJ & Jell RM. (1992). Stimulus velocity dependence of human vertical optokinetic nystagmus and afternystagmus. *J Vestib Res* **2,** 99-106.

Westall CA, Eizenman M, Kraft SP, Panton CM, Chatterjee S & Sigesmund D. (1998). Cortical binocularity and monocular optokinetic asymmetry in early-onset esotropia. *Invest Ophthalmol Vis Sci* **39,** 1352-1360.

Westall CA & Shute RH. (1992). OKN asymmetries in orthoptic patients: contributing factors and effect of treatment. *Behav Brain Res* **49,** 77-84.

Wong AM. (2004). Listing's law: clinical significance and implications for neural control. *Surv Ophthalmol* **49,** 563-575.

Wright KW. (1996a). Clinical optokinetic nystagmus asymmetry in treated esotropes. *Journal of Pediatric Ophthalmology & Strabismus* **33,** 153-155.

Wright KW. (1996b). Clinical optokinetic nystagmus asymmetry in treated esotropes. *J Pediatr Ophthalmol Strabismus* **33,** 153-155.

Yee RD, Baloh RW & Honrubia V. (1980). Study of congenital nystagmus: optokinetic nystagmus. *Br J Ophthalmol* **64,** 926-932.

Zackon DH & Sharpe JA. (1987). Smooth pursuit in senescence. Effects of target acceleration and velocity. *Acta Otolaryngol* **104,** 290-297.

Zee DS, Chu FC, Leigh RJ, Savino PJ, Schatz NJ, Reingold DB & Cogan DG. (1983). Blink-saccade synkinesis. *Neurology* **33,** 1233-1236.

Zeki S, Watson JD, Lueck CJ, Friston KJ, Kennard C & Frackowiak RS. (1991). A direct demonstration of functional specialization in human visual cortex. *J Neurosci* **11,** 641-649.