HORIZONTAL AND VERTICAL OPTOKINETIC NYSTAGMUS IN NORMAL AND ABNORMAL INFANTS AND ADULTS

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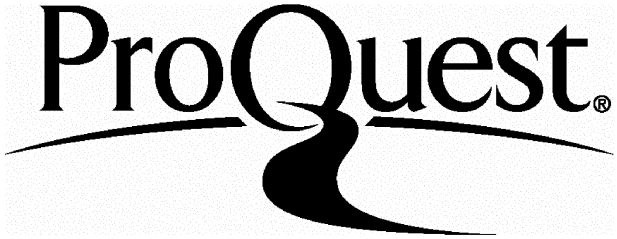

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Abstract

Optokinetic nystagmus (OKN) is a reflexive visual response that can be elicited from humans of all ages. The optokinetic response consists of an alternating sequence of following movements (slow phases) in the direction of stimulus movements, interrupted by fast movements (quick phases) in the opposite direction. This thesis investigates how the slow and the quick phases of both horizontal and vertical OKN may have a role in the assessment of the oculomotor system.

In normal adults, the speeds of horizontal OKN quick phases were compared to horizontal saccades. It was found that they had the same main sequence for duration but that the main sequence for peak velocity is slightly faster for saccades than OKN quick phases. Also, the speeds of horizontal OKN quick phases in normal infants were considered and found not to be significantly different ($p>0.05$) to those of adults. Further, the horizontal OKN quick phases in a group of children with neuronopathic Gaucher disease were examined. It was found that horizontal saccades and horizontal OKN quick phases were grossly slow in this condition. It is proposed that examination of OKN quick phases is a simple clinical means for approximating the saccadic main sequence and for identifying patients with brainstem abnormalities.

Gaze position during full-field horizontal OKN stimulation was assessed. It was confirmed that the mean position of gaze is shifted in the direction opposite to stimulus movement. This was a robust phenomenon occurring even at very low stimulus speeds (2°/s). An explanation for this behaviour is proposed based on observations from patients with a vestibulocerebellar disorder. In this theory a leaky neural integrator is used to enhance velocity-matching.

We also investigated the characteristics of vertical OKN and vertical saccades in normal adult subjects. We found that for amplitudes up to 20° there were no statistical differences between vertical centripetal and centrifugal saccades and no differences in the durations or peak velocities of upward and downward saccades. On the other hand, vertical saccades were significantly slower than horizontal saccades and vertical OKN quick phases were significantly slower than vertical saccades. We found that vertical OKN gain was asymmetrical: upward OKN gain was greater than downward OKN gain by an average of 0.08.

Vertical OKN was also studied in adults with strabismus and infants and children with neurological abnormalities. The patients with strabismus often

demonstrated a similar asymmetry of vertical OKN as seen in control subjects, with upward OKN stimulus motion eliciting a higher gain, although the gain was usually lower and the responses were very variable. In infants and children, abnormal vertical OKN was found in those who had either a neurometabolic disease or an abnormality of the cortex, brainstem and/or cerebellum.

It is concluded that OKN testing has an important role in the assessment of the oculomotor system both as a visual response and as a motor behaviour.

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Abbreviations

CN	Congenital nystagmus
CNS	Central nervous system
DAT	Digital audio tape
DC	Direct current
DLPN	Dorsolateral pontine nucleus
DVM	Delayed visual maturation
EOG	Electro-oculography
ERT	Enzyme replacement therapy
FEF	Frontal eye fields
FEM	Fast eye movements
FIR	Finite impulse response
GD	Gaucher disease
HSIF	Horizontal saccade initiation failure
INC	Interstitial nucleus of cajal
IR	Infrared limbal reflection
LED	Light emitting diode
LN	Latent nystagmus
LTN	Lateral terminal nucleus
MANOVA	Multivariate analysis of variance
mHOKN	Monocular horizontal optokinetic nystagmus
MLF	Medial longitudinal fasciculus
MLN	Manifest latent nystagmus
MRF	Mesencephalic reticular formation
MRI	Magnetic resonance imaging
MST	Middle superior temporal
MT	Middle temporal
MVN	Medial vestibular nuclei
NOT	Nucleus of the optic tract
NPH	Nucleus prepositus hypoglossi
NS	Normal subjects
N-T	Nasal to temporal
OKAN	Optokinetic afternystagmus
OKN	Optokinetic nystagmus

OKNd	Delayed optokinetic nystagmus
OKNe	Early optokinetic nystagmus
PPRF	Paramedian pontine reticular formation
riMLF	Rostral interstitial nucleus of the medial longitudinal fasciculus
SIF	Saccade initiation failure
T-N	Temporal to Nasal
VEP	Visually evoked potential
VN	Vestibular nystagmus
VOR	Vestibulo-ocular reflex
VSIF	Vertical saccade initiation failure

Chapter 1 - Introduction

1.1 An introduction to optokinetic nystagmus

Optokinetic nystagmus (OKN) is a reflexive oscillation of the eyes induced by motion of the visual field. Purkinje (1825) was the first to describe this response, having observed it in spectators at a cavalry parade. The function of the optokinetic system, together with the vestibular system, is to hold images steadily on the retina during movements of the head or body (Leigh and Zee, 1999).

OKN can be elicited even from the newborn and is virtually impossible to suppress if the whole visual field moves. Therefore, it has a potentially important role to play in the clinical assessment of infants and children. A considerable, if somewhat controversial, literature has emerged attempting to relate OKN development, particularly the monocular response, to various other factors e.g. the development of binocularity, cortical development, visual deprivation and esotropia. Unfortunately, this has drawn attention away from the useful clinical role of this reflexive behaviour. In this thesis we will explore the clinical uses of the optokinetic response. Firstly, in this chapter, we will review the important neurophysiological aspects of OKN, discuss its development and consider what are currently thought to be the clinical uses of this reflexive response.

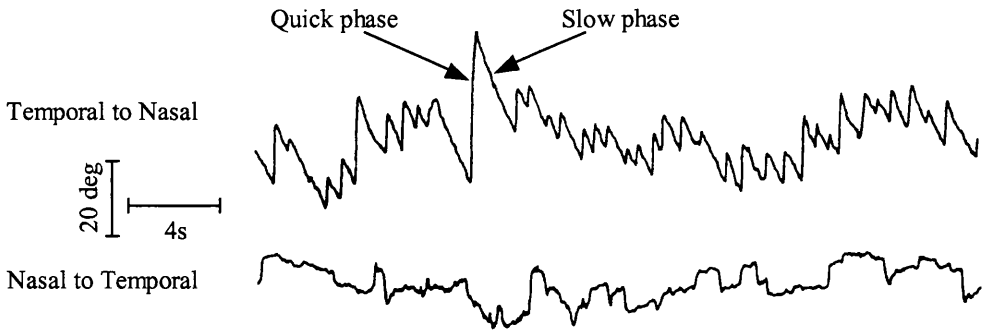
1.2 The optokinetic response

OKN consists of an alternating sequence of slow and quick (fast) phases and when recorded the waveform has a characteristic irregular saw-tooth appearance

(Figure 1.1). During the slow phase the eyes follow the stimulus to minimise the slippage of the image across the retina. The effectiveness of OKN in reducing retinal image slip may be indicated by the ratio of slow phase eye velocity to stimulus velocity, which is termed the 'gain'. If eye velocity precisely matches the stimulus velocity then the gain is unity, but typically the eyes do not quite keep up with the stimulus so the gain is usually less than 1. In normal subjects OKN gain decreases with increasing stimulus velocity (Dichgans *et al.*, 1973; Hood, 1975; van Die and Collewijn, 1982; van den Berg and Collewijn, 1988; Holm-Jensen and Peitersen, 1997) and with ageing (Simons and Büttner, 1985; Ura *et al.*, 1991; Baloh *et al.*, 1993; Paige, 1994). Vertical optokinetic responses tend to be of lower gain than horizontal responses (Böhmer and Baloh, 1991). A greater gain for upward stimulus motion than for downward stimulus motion has been reported by some investigators (van den Berg and Collewijn, 1988; Murasugi and Howard, 1989; Ogino *et al.*, 1996) although others have established no systematic differences (Böhmer and Baloh, 1991).

It might be thought that the quick phases of OKN would simply re-centre the eyes to prevent the slow phases from taking the eyes into the mechanical limits. This is not the case, the quick phases of horizontal OKN actually take the eye into the direction from which the motion originated (the opposite direction to stimulus movement) and can occur before the slow phase has even brought the eyes back to the midline (Chun and Robinson, 1978).

Figure 1.1 Monocular horizontal OKN response from a strabismic patient



Monocular horizontal OKN elicited by a full-field curtain from an 11-year-old subject with strabismus and no stereopsis, viewing with her right eye. Note there is no OKN in the nasal to temporal direction, which is abnormal for this age (see text). By convention on the trace an upward deflection indicates eye movement to the right.

1.2.1 Early and delayed horizontal OKN

In primates two distinct components participate in the generation of the horizontal OKN slow phase response:

1) Early (direct, fast) OKN (OKNe) leads to the fast build-up of slow phase velocity so that maximum velocities are reached in about 0.5s in humans (Abadi *et al.*, 1994). It is also responsible for the fast drop of slow phase velocity (in the light) at the end of stimulation.

2) Delayed (indirect, slow) OKN (OKNd) has a more sluggish response which, during continuous stimulation, leads to a gradual build-up of slow phase velocity to steady-state eye velocity. OKNd is also responsible for the slow decay of velocity in the dark, which is known as optokinetic afternystagmus (OKAN).

In animals with poor foveal vision (e.g. cat) or no foveal vision (e.g. rabbit) only OKNd is present (Collewijn, 1972; Evinger and Fuchs, 1978; Fuller, 1985). In the monkey, both OKNe and OKNd are well developed (Cohen *et al.*, 1977). The initial jump of slow phase velocity at stimulus onset indicates OKNe. OKNd is shown

by the gradual build-up of slow phase velocity towards stimulus velocity which follows the initial jump and by the OKAN that is seen on cessation of the stimulus. When healthy human adults are exposed to optokinetic stimulation both OKNe and OKNd are activated. However, OKNe is completely dominant in the light and, therefore, during optokinetic stimulation the slow phase velocity rapidly approaches stimulus velocity and does not show gradual build-up. The presence of OKNd can only be revealed by looking for OKAN in the dark. However, in patients with lesions of their OKNe system, OKNd may be exposed during optokinetic stimulation in the light. For example, a slow build-up of OKN has been reported in patients with lesions of the parietal lobe (Baloh *et al.*, 1982) and in patients with vestibulocerebellar disorders (Zee *et al.*, 1976b; Baloh *et al.*, 1981; Harris *et al.*, 1993b).

In infants horizontal OKN has been found to have a fast build-up of slow phase velocity from at least 1 month of age (Hainline *et al.*, 1984a; Harris *et al.*, 1994). This indicates that infants too demonstrate OKNe from an early age.

1.2.2 Look-OKN and stare-OKN

A further important consideration when testing OKN is that in humans the response differs depending on the attentional state of the subject. Ter Braak (1936) distinguished between 'look-OKN' ('schau-nystagmus') and 'stare-OKN' ('stier-nystagmus'). Look-OKN is elicited by instructing the subject to pay attention to single details in the moving stimulus. The OKN exhibited has a high gain, large-amplitude slow phases and infrequent quick phases (Honrubia *et al.*, 1968). In contrast, stare-OKN is elicited by instructing the subject to look passively at the stimulus, without any deliberate attempt to pay attention to specific features. Stare-OKN has a lower gain, lower amplitude and more frequent quick phases (Honrubia *et*

al., 1968). The different characteristics of look-OKN and stare-OKN may be caused by the greater activation of the smooth pursuit system in look-OKN (Pola and Wyatt, 1993).

1.2.3 The role of central versus peripheral retina

The position of the stimulus on the retina can influence the optokinetic response. It is generally believed that the central retina dominates in the production of horizontal OKN. A central stimulus, almost regardless of size, elicits horizontal OKN with a high gain that is only slightly below that for full-field motion. On the other hand, the response to a peripheral stimulus is much diminished or even abolished (van Die and Collewijn, 1982; Howard and Ohmi, 1984; Murasugi *et al.*, 1986; Abadi and Pascal, 1991). The dominance of the central retina has been further shown by the simultaneous presentation of central and peripheral movement in opposite directions (Brandt *et al.*, 1973; Abadi and Pascal, 1991). These studies found that the horizontal OKN elicited is determined by the direction of the central movement. However, if the central and peripheral fields move in the same horizontal direction but at different speeds, the optokinetic response is driven by whichever field moves slower (Abadi and Pascal, 1991).

The effect of central visual field loss from pathologically or artificially induced central scotomas has also been investigated. Only a slight reduction of horizontal OKN due to pathological central scotomas of less than 15° has been reported (Yee et al., 1982; van Die and Collewijn, 1986; Abadi and Pantazidou, 1997). A statistically significant reduction in OKN gain has been reported for central scotomas of more than 20° at stimulus velocities of 30, 45, and 60°/s, but not at a stimulus velocity of 15°/s (Valmaggia *et al.*, 2001). These studies demonstrate that

complete integrity of the central retina is not essential for the generation of high OKN gains and that the peripheral retina is important in the generation of OKN.

On the other hand, using artificially induced central scotomas, some investigators have reported a large reduction in horizontal OKN gain even for small scotomas (Cheng and Outerbridge, 1975; Miyoshi *et al.*, 1978; Gresty and Halmagyi, 1979; Dubois and Collewijn, 1979a; van Die and Collewijn, 1982). However, in studies with artificial scotomas the edge of the mask used to create the central field loss is likely to contribute to the suppression of OKN (Howard and Ohmi, 1984; Abadi *et al.*, 1994). Further, in experiments with retinal stabilised scotomas, the scotoma itself is seen to move and can become a stimulus for further movement or can be stared at while the optokinetic stimulus is neglected (Gresty and Halmagyi, 1979).

1.2.4 OKN versus smooth pursuit

It has been suggested that the slow phase of OKN is in fact a smooth pursuit response. However, although smooth pursuit and OKN (especially OKNe) may share a similar neural pathway, and thus lesions that affect smooth pursuit may also affect OKN, there are important distinctions between the two. The first distinction concerns the function of each response. OKN helps to stabilise the entire retinal image during head-turning or locomotion. Smooth pursuit, on the other hand, is concerned with the foveation of usually small targets moving on a stationary, textured background. Consequently OKN is seen in all animals with ocular motility whereas smooth pursuit is found only in species with a fovea (Collewijn, 1969; Dubois and Collewijn, 1979b; Robinson, 1981). Secondly, OKN is involuntary (Rademaker and Ter Braak, 1948) whereas smooth pursuit is voluntary to a considerable degree (Rashbass, 1961; Barnes

and Hill, 1984; Pola and Wyatt, 1985; Wyatt and Pola, 1987). Thirdly, when a human infant views a full-field horizontal optokinetic stimulus with both eyes open OKN can easily be elicited (Dayton and Jones, 1964; Kremenitzer *et al.*, 1979; Schor *et al.*, 1983) whereas the response to a horizontal smooth pursuit stimulus is much poorer or absent (McGinnis, 1930; Dayton *et al.*, 1964; Dayton and Jones, 1964; Kremenitzer *et al.*, 1979; Aslin, 1981; Roucoux *et al.*, 1983; Shea and Aslin, 1984; Jacobs *et al.*, 1997). Further, in infants with delayed visual maturation a complete dissociation between horizontal OKN and horizontal smooth pursuit is evident, as during the early period of visual unresponsiveness only OKN can be elicited (Harris *et al.*, 1996a).

Finally, in monkeys, following bilateral occipital lobectomies, OKNe and smooth pursuit eye movements were eliminated but the recovery of OKNe and smooth pursuit occurred with different time courses (Zee *et al.*, 1987).

1.3 The neural generation of OKN

1.3.1 Horizontal OKN pathways

As discussed in 1.2.1, in primates the optokinetic response has two components, OKNe and OKNd. Figure 1.2 illustrates the basic neural pathway for the generation of both of these components. OKNe is mediated by a cortico-ponto-cerebellar neural pathway that is similar to the smooth pursuit pathway (Fuchs and Mustari, 1993). This includes the middle superior temporal area of the cortex and the dorsolateral pontine nucleus of the brainstem, which project to the oculomotor centres via the cerebellum. The nucleus of the optic tract in the pretectum is a centre for retinal slip and may provide an error signal for the internal control of

OKNe and smooth pursuit. However, it is probably not in the direct cortico-ponto-cerebellar pathway.

OKNd is mediated by a "direct" retino-pretectal pathway. OKNd depends on stimulation of motion-sensitive cells in the retina (Oyster and Barlow, 1967; Dowling, 1975; Rodieck, 1979) that project via the accessory optic tract to cells in the NOT (Collewijn, 1975). OKNd charges the velocity storage mechanism in the brainstem.

In the following section we will consider in more detail the principal areas involved in the control of horizontal OKN.

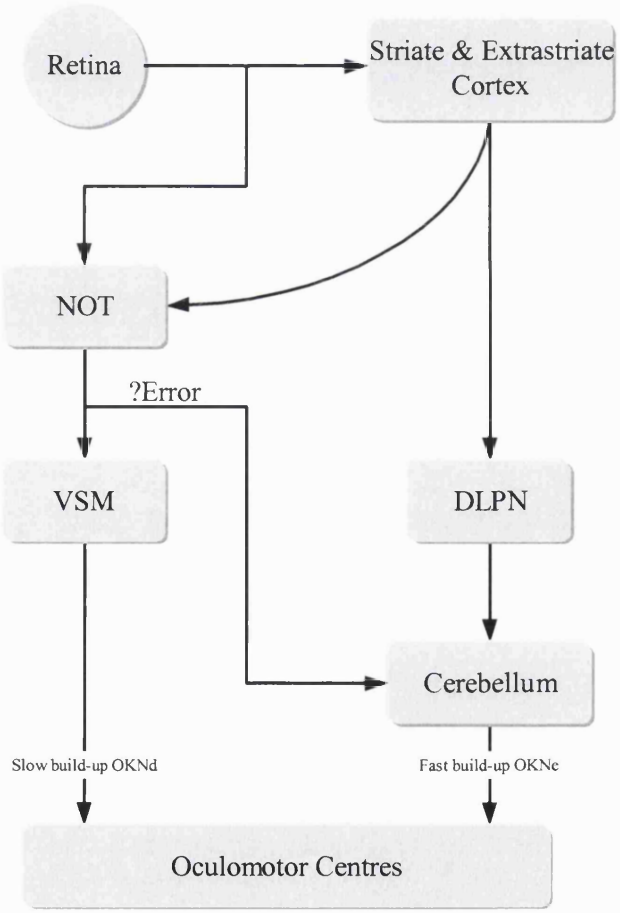


Figure 1.2. Horizontal OKN pathways

Schematic diagram showing the basic pathways responsible for both components of horizontal OKN. OKNe is mediated by a cortico-ponto-cerebellar pathway and OKNd is mediated by a retino-pretectal pathway. NOT: nucleus of the optic tract; VSM: velocity storage mechanism; DLPN: dorsolateral pontine nucleus; OKNd: delayed OKN; OKNe: early OKN.

1.3.1.1 Cortical contributions to horizontal OKN

The striate visual cortex (V1) is probably the first cortical area in the OKNe pathway since lesions in V1 impair the initial rapid rise in OKN gain. Also, following lesion of V1, OKNd is poor (low and variable gain) for high stimulus velocities and horizontal OKN is asymmetric when tested monocularly, with temporal to nasal stimulus motion producing a significantly better response than motion in the opposite direction (Zee *et al.*, 1987). This asymmetry is like that seen in afoveate mammals whose cortices apparently contribute little to OKN (Simpson, 1984).

Area V5, a region in the superior temporal sulcus specialised in visual motion, is also involved in horizontal OKN control. Both the middle temporal (MT) and the medial superior temporal (MST) areas are located in the V5 complex. The human homologue of V5 is considered to be in the lateral occipitotemporal cortex, at the border between Brodmann areas 19 and 37 (Zeki *et al.*, 1991; Watson *et al.*, 1993).

MT cortex

Neurons in the macaque MT cortex respond to motion in all directions and are sensitive to stimulus velocities ranging from 10 to 200°/s (Maunsell and Newsome, 1987). Since the MT cortex contains units that are sensitive to both the velocity and direction of visual motion, it could contribute to both OKNe and OKNd. Unfortunately, OKN has not been tested in animals with lesions restricted to MT. However, it is known that some MT units discharge during smooth pursuit (Komatsu and Wurtz, 1988) and small chemical lesions impair a monkey's ability to match the speed of his smooth pursuit eye movements to the speed of the moving target (Newsome *et al.*, 1985).

MST cortex

Area MT projects heavily to neighbouring area MST (Fuchs and Mustari, 1993). Like many units in MT, those in MST are sensitive to both the velocity and the direction of moving stimuli. Many MST neurons prefer large-field moving stimuli and respond during optokinetic stimulation (Kawano *et al.*, 1994) as well as during smooth pursuit (Komatsu and Wurtz, 1988). All directions of visual motion are represented.

MST lesions in monkeys produce deficits in both ipsiversive OKNe and OKNd at higher velocities (Dürsteler and Wurtz, 1988). In humans ipsiversive horizontal OKN is disrupted following lesions deep in the white matter located near the temporoparieto-occipital junction (Kömpf, 1986; Incoccia *et al.*, 1995; Heide *et al.*, 1996; Schenk and Zihl, 1997). This localisation is consistent with that of the presumed human homologue of V5 (see above).

1.3.1.2 The nucleus of the optic tract

The nucleus of the optic tract (NOT) lies in the pretectum. The visual sensitivity of units in the NOT is derived from contralateral retinal inputs (Hoffmann and Stone, 1985) and ipsilateral striate and extrastriate visual cortical inputs (Baleydier *et al.*, 1990; Hoffmann *et al.*, 1992; Mustari *et al.*, 1994).

The initial rapid rise of OKN (OKNe) survives NOT lesions and is not elicited by NOT stimulation. On the other hand, OKNd fails to recover following large lesions of the NOT and electrical stimulation of the NOT elicits nystagmus which is very similar to natural OKNd and OKAN (Fuchs and Mustari, 1993). Thus, the NOT is believed to have a pivotal role in the production of OKNd and, therefore, it is suggested that the principal pathway for OKNd is subcortical (Figure 1.2).

Each NOT functions independently and neurons in the NOTs respond only to ipsilateral stimuli (Mustari and Fuchs, 1989; Fuchs and Mustari, 1993) of up to 60°/s (Mustari and Fuchs, 1989; Ilg and Hoffmann, 1996). Thus, unilateral NOT lesions affect only OKN slow phases toward the side of the lesion (Kato *et al.*, 1988). The left and right NOTs operate in a push-pull fashion and any imbalance between their spontaneous activity causes the eyes to drift in the direction of the more active NOT (Hoffmann, 1982).

Neurons in the primate NOT have large receptive fields appropriate for encoding full-field motion and respond briskly during OKN. The slow build-up in eye velocity during OKN (OKNd) is thought to be due to the charging of a velocity storage mechanism (Raphan *et al.*, 1997). The NOT could provide inputs to the velocity storage mechanism through projections to the medial vestibular nucleus and nucleus prepositus hypoglossi (Magnin *et al.*, 1983; Belknap and McCrea, 1988; Mustari *et al.*, 1994; Büttner-Ennever *et al.*, 1996). The NOT also has a dense projection to the dorsal cap of Kooy in the inferior olive, which is the major source of climbing fibre input to the flocculus of the vestibulocerebellum.

1.3.1.3 The dorsolateral pontine nucleus

In addition to its input from extrastriate cortex (May and Andersen, 1986) the dorsolateral pontine nucleus (DLPN) also receives a sparse projection from the NOT (Mustari *et al.*, 1990). The DLPN has efferent connections with the cerebellar flocculus and vermis (Langer *et al.*, 1985).

Lesion studies implicate the DLPN in OKNe (May *et al.*, 1988; Kawano *et al.*, 1990). Chemical lesions of the DLPN severely reduce OKNe for motion toward the side of the lesion. However, following a DLPN lesion eye velocity reaches drum

velocity after about 15s and OKAN is present. This indicates that DLPN lesions have little effect, if any, on OKNd.

1.3.1.4 The velocity storage mechanism

The velocity storage mechanism of the brainstem is responsible for the mediation of horizontal OKN and the velocity storage mechanism of the cerebellum is responsible for the modulation of horizontal OKN.

The velocity storage mechanism of the brainstem lies in the medial vestibular nuclei (MVN) and the nucleus prepositus hypoglossi (NPH) (Cannon and Robinson, 1987; Mettens *et al.*, 1994). The vestibular commisure also seems to be important for velocity storage as sectioning of this structure abolishes OKAN (Wearne *et al.*, 1997). The velocity storage mechanism also must require a viable vestibular nerve input since it has been shown that bilateral labyrinthectomy permanently eliminates or severely attenuates OKAN in both monkeys and man (Zee *et al.*, 1976a).

1.3.1.5 Cerebellar contributions to horizontal OKN

Evidence from lesions and recordings indicate that the cerebellum is involved in the production of both components of horizontal OKN. The flocculus and nodulus/uvula are known to receive visual inputs via mossy and climbing fibre routes and studies have generally concentrated mainly on these areas.

The flocculus

In the monkey, bilateral lesions that involve the flocculus and parts of the paraflocculus severely attenuate OKNe but leave the velocity storage mechanism

responsible for OKNd largely intact (Zee *et al.*, 1981; Waespe and Henn, 1987). Thus, when using prolonged unidirectional test stimuli, various deficits in OKN are evident. Firstly, there is a marked reduction in OKNe (50-90%). Secondly, although it takes longer to achieve them, the steady-state OKN response is normal for lower stimulus velocities up to 45-60°/s but, for higher stimulus velocities, peak eye velocity saturates at about 60°/s. Thirdly, OKAN is normal except for the almost total elimination of the initial rapid drop in eye speed when the lights are first extinguished.

The nodulus/uvula

In monkeys, especially at high drum speeds, removal of the nodulus and uvula is associated with impairment of horizontal OKN but mainly affects OKNd (Igarashi *et al.*, 1975). In the lesioned animal OKAN is found to be abnormal in three major respects: (1) OKAN no longer shows, with repeated exposure to optokinetic stimulation, the usual progressive reduction in time constant (habituation); (2) OKAN dumping, either by exposure to a stationary visual pattern or by tilting, is impaired; (3) OKAN often shows periodic reversals (Waespe *et al.*, 1985; Cohen *et al.*, 1987).

In contrast to these effects on OKNd, nodular/uvular lesions have no effect on OKNe. Similarly, lesions of the flocculus do not affect dumping of OKAN, whether it be by tilt or by fixation of a stationary scene (Waespe and Henn, 1987).

1.3.2 Vertical OKN pathways

The neural pathways controlling vertical OKN have not been clearly established. However, by considering the neural pathways controlling vertical saccades and vertical smooth pursuit we can go some way towards explaining the neural control of vertical OKN.

1.3.2.1 The neural generation of vertical saccades

The frontal eye fields and superior colliculi are responsible for the generation of vertical (and horizontal) saccades (Miller, 1985). Although from here the pathways controlling vertical saccades have not been fully elucidated, it is believed that before reaching the vertical oculomotor nuclei they are relayed via the rostral interstitial nuclei of the medial longitudinal fasciculus (riMLF). This pair of nuclei in the rostral midbrain contain vertical saccade burst neurons (both excitatory and inhibitory) and thus are crucial for the generation of vertical saccades (Büttner-Ennever, 1979; Büttner-Ennever *et al.*, 1982; Moschovakis *et al.*, 1991a; Moschovakis *et al.*, 1991b). Some electrophysiologic and anatomic studies have suggested that, although excitatory and inhibitory burst units are intermingled, neurons projecting to muscles that depress the eye (inferior rectus and superior oblique) may be located more rostrally, whereas neurons projecting to muscles that elevate the eye (superior rectus and inferior oblique) lie more caudally (Kömpf *et al.*, 1979; Wang and Spencer, 1996). On the other hand, Büttner-Ennever and colleagues (Büttner-Ennever *et al.*, 1982) suggested that the medial aspect of the riMLFs contain neurons involved in upgaze while neurons from the lateral portion are primarily involved in downgaze.

However, others have reached opposite conclusions to this (Pierrot-Deseilligny *et al.*, 1982).

Each burst neuron in the riMLFs projects monosynaptically to ocular motoneurons supplying yoke muscle pairs so that the eyes are tightly yoked during vertical saccades (Moschovakis *et al.*, 1990). Saccadic innervation from the riMLFs is unilateral to depressor muscles but bilateral to elevator muscles with axons crossing within the oculomotor nucleus (Moschovakis *et al.*, 1991a; Moschovakis *et al.*, 1991b).

In addition to the direct projections to vertical ocular motoneurons in the oculomotor (IIIrd) nucleus and trochlear (IVth) nucleus, vertical excitatory burst neurons in the riMLFs send axon collaterals to the interstitial nucleus of Cajal (INC) (Moschovakis *et al.*, 1991a; Moschovakis *et al.*, 1991b). The INC is an important component of the velocity-to-position integrator for vertical (and torsional) eye movements (Leigh and Zee, 1999).

Although the riMLFs are the key structure for vertical saccades, some vertical burst neurons lie outside their boundaries. The central mesencephalic reticular formation (MRF), in particular, seems to play an important role in the generation of vertical saccades (Waitzman *et al.*, 2000a; Waitzman *et al.*, 2000b).

1.3.2.2 The neural generation of vertical smooth pursuit

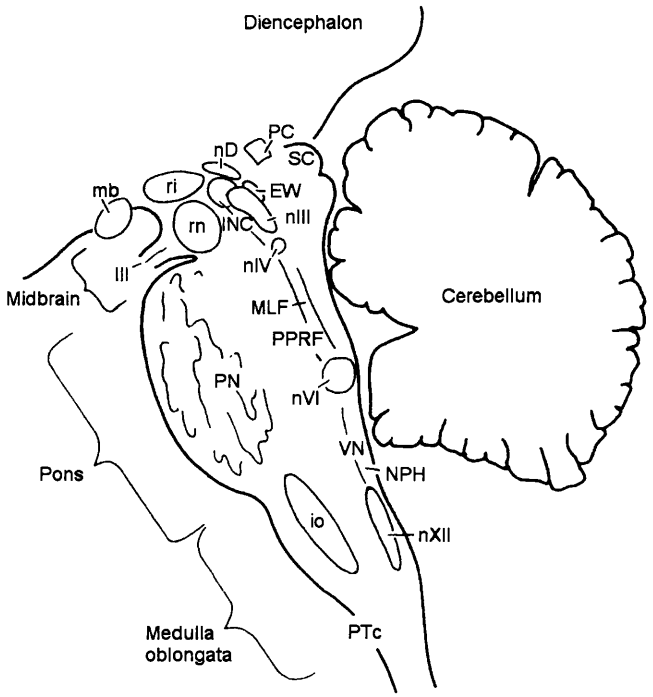
The pathways responsible for vertical smooth pursuit most likely originate in the posterior hemisphere (Miller, 1985) but, again, the pathways to the vertical oculomotor nuclei are not fully understood. In the monkey, at least, the DLPN are considered to be a crucial relay since following unilateral DLPN lesions vertical and horizontal smooth pursuit are impaired (May *et al.*, 1988). It is thought that the

flocculus of the cerebellum is likely to be involved since bilateral flocculectomy results in major abnormalities in the slow phases of vertical OKN and horizontal OKN (Waespe *et al.*, 1983). Axons in the medial longitudinal fasciculus (MLF) carry, from medulla to midbrain, neural signals which are important for vertical smooth pursuit, vertical vestibular eye movements and, to a lesser extent, the vertical gaze holding command (King *et al.*, 1976; Pola and Robinson, 1978; Tomlinson and Robinson, 1984; McCrea *et al.*, 1987). The MLF is the most important route for these projections, but the brachium conjunctivum and other pathways are also involved (Büttner-Ennever and Büttner, 1992; Cremer *et al.*, 1999). It is also known that neurons that discharge in relation to vertical pursuit can be found in the dentate nucleus and in the Y-group of the vestibular nuclei which caps the inferior cerebellar peduncle (Chubb and Fuchs, 1981; Chubb and Fuchs, 1982).

Although the final supranuclear relay in the midbrain reticular formation has not been identified, the INC is considered to play an important role in the control of vertical smooth pursuit (Pierrot-Deseilligny *et al.*, 1989). The INC projects to vertical motoneurons in the oculomotor and trochlear subnuclei on the contralateral side of the brainstem via the posterior commissure (Kokkoroyannis *et al.*, 1996).

Thus, we can infer that the neural pathways controlling vertical OKN most probably involve the cortex, brainstem (particularly the rostral midbrain) and cerebellum and, therefore, abnormalities of these areas could result in abnormal vertical OKN.

Figure 1.3. The human brainstem



A sagittal view of the human brainstem showing the location of structures important in the control of vertical and horizontal OKN. The areas referred to in the text are: III = oculomotor nerve; INC = interstitial nucleus of Cajal; io = inferior olive; MLF = medial longitudinal fasciculus; nIII = oculomotor nucleus; nIV = trochlear nerve; nVI = abducens nucleus; PC = posterior commissure; PN = pontine nuclei; NPH = nucleus prepositus hypoglossi; PPRF = paramedian pontine reticular formation; ri = rostral interstitial nucleus of the MLF; SC = superior colliculus; VN = vestibular nuclear complex. Other areas shown: EW = Edinger-Westphal nucleus; mb = mammillary body; nD = nucleus of Darkschewitsch; PTc = pyramidal tract decussation; rn = red nucleus. Adapted from Büttner-Ennever and Büttner, 1992.

1.4 Development of OKN

1.4.1 Development of horizontal OKN

Throughout this thesis the term 'bi-ocular OKN' refers to the response to an optokinetic stimulus viewed with both eyes open and does not have any implication of binocularity per se. In normal, full-term, human infants full-field bi-ocular horizontal OKN has been found to be present from birth (Dayton and Jones, 1964; Kremenitzer *et al.*, 1979; Schor *et al.*, 1983).

1.4.1.1 Monocular asymmetries

Adult humans, monkeys and cats usually show symmetrical, or nearly symmetrical, horizontal OKN when tested monocularly (mHOKN): mHOKN is easily elicited by a stimulus moving in the temporal to nasal direction (T-N) of the viewing eye and by a stimulus moving in the nasal to temporal direction (N-T) (Pasik and Pasik, 1964; Braun and Gault, 1969; Schor and Levi, 1980). However, in young human infants, young monkeys and young kittens mHOKN is asymmetrical. The beat frequency and the speed and amplitude of the slow phases are lower when the stimulus moves in the N-T direction of the viewing eye than they are in the T-N direction (Atkinson, 1979; Atkinson and Braddick, 1981; Naegele and Held, 1982; Schor *et al.*, 1983; Naegele and Held, 1983; van Hof-van Duin and Mohn, 1984; van Hof-van Duin and Mohn, 1985; van Hof-van Duin and Mohn, 1986a; Roy *et al.*, 1989; Lewis *et al.*, 1992; Harris *et al.*, 1994). With increasing age, the mHOKN response gradually becomes symmetrical. In contrast, other species such as the rabbit, guinea pig, gerbil, rat, some birds and some lizards, exhibit a permanent bias in the mHOKN response for stimulus movement in the T-N direction (Huizinga and Meulen, 1951; Tauber and Atkin, 1968; Collewijn, 1969). However, with both eyes open this asymmetry will not be evident since one eye will always yield a T-N response.

In kittens, the monocular response to stimuli moving in the N-T direction develops on average 9-16 days after the response to stimuli moving in the T-N direction (van Hof-van Duin, 1978). In monkeys this period is approximately 14-21 days (Atkinson, 1979). A number of investigators have attempted to determine the age at which mHOKN becomes symmetrical in human infants. Originally, it was suggested that symmetry was attained by 3-5 months of age (Atkinson, 1979;

Atkinson and Braddick, 1981; Naegele and Held, 1982; Naegele and Held, 1983; van Hof-van Duin and Mohn, 1984; van Hof-van Duin and Mohn, 1985; van Hof-van Duin and Mohn, 1986a). However, it has since been found that although the asymmetry in mHOKN declines over the first six months of life when moderate stimulus speeds are used for testing (26 and 34°/s), it may persist beyond six months at higher stimulus speeds (above 45°/s) (Roy *et al.*, 1989; Harris *et al.*, 1994). Thus, it appears that in human infants the N-T response saturates at a lower speed than the T-N response, so the monocular asymmetry depends not only on age but also on stimulus speed. Therefore, the conclusion reached by some that symmetry occurs between 3 and 5 months of age probably resulted from the limited range of stimulus speeds used.

In cats the response to stimuli moving in the T-N direction is believed to be at least partially mediated by a subcortical pathway, while the response in the reverse direction relies almost exclusively on a cortical pathway (Wood *et al.*, 1973; Hoffmann and Schoppmann, 1975; Hoffmann, 1979). It has been suggested that in the immature kitten horizontal OKN is initially mediated subcortically and it is only with the development of the visual cortex, and thus the maturation of the cortical pathway, that mHOKN becomes symmetrical (Hoffmann, 1982).

It has been proposed that human infants show asymmetrical mHOKN because, as in young kittens, initially horizontal OKN is mediated by a subcortical pathway (Hoffmann, 1989; Lewis *et al.*, 1989; Lewis *et al.*, 2000). However, this is unlikely since, as already mentioned, horizontal OKN in human infants has been found to have a fast build-up of slow phase velocity from at least 1 month of age (Hainline *et al.*, 1984a; Harris *et al.*, 1994). This implies that OKNe is probably functioning from at least 1 month of age and that there is cortical mediation of horizontal OKN. So it

would seem that a more likely explanation for asymmetrical mHOKN in human infants is that the retino-cortical pathways mature earlier for T-N motion than for N-T motion (Harris *et al.*, 1996a).

1.4.1.2 Relation to visual experience

It has been shown, in both animals and humans, that the development of symmetrical mHOKN is greatly affected by *abnormal* visual experience early in life. If normal visual development is interrupted by unequal visual inputs, due to strabismus and/or anisometropia or a monocular congenital cataract, the mHOKN asymmetry seen in healthy neonates often persists (Figure 1.1) (Schor and Levi, 1980; Maurer *et al.*, 1983; Naegele and Held, 1983; Hine, 1985; Westall and Schor, 1985; van Hof-van Duin and Mohn, 1986a; Bourron-Madignier *et al.*, 1987; Demer and von Noorden, 1988; Westall *et al.*, 1989; Lewis *et al.*, 1989; Westall and Shute, 1992; Schor *et al.*, 1997; Westall *et al.*, 1998). In humans, when the abnormal visual experience is of early onset (before 2 years of age) the asymmetry is usually present in both eyes (Westall and Shute, 1992). If it is of late onset, asymmetrical mHOKN is less likely to persist (Schor and Levi, 1980; Maurer *et al.*, 1983) and if it does occur it is probable that only one eye will be affected (Westall and Shute, 1992). Although the most characteristic impairment of mHOKN is the persistence of the asymmetry seen in the neonate, the mHOKN response to stimulation in the T-N direction may also be impaired, especially at higher stimulation velocities in a grossly amblyopic eye (Schor and Levi, 1980; Mohn *et al.*, 1986; van Hof-van Duin and Mohn, 1986b).

The persistence of mHOKN asymmetry along with poor binocularity in humans and animals who have been subject to abnormal visual experience early in life and the detection of binocular function at approximately the same time as the

attainment of mHOKN symmetry in human infants, has led a number of investigators to suggest a link between the development of symmetrical mHOKN and binocularity. There are, however, a number of reasons to believe that this may not be causal. Firstly, some studies suggest that the development of symmetrical mHOKN and binocularity do *not* follow the same time course. For example, a longitudinal study of 105 infants by Wattam-Bell and co-workers (Wattam-Bell *et al.*, 1987) found that the development of binocularity, measured by visually-evoked potentials to a dynamic random dot correlogram, did *not* closely match the development of symmetrical mHOKN. In their study there was a group of infants who had grossly symmetrical OKN at a time when they showed no evidence of functional binocularity. Furthermore, as discussed earlier, if high stimulus speeds are used, the time course for the development of mHOKN symmetry lasts well beyond the age at which normal binocularity has developed (Roy *et al.*, 1989; Harris *et al.*, 1994). Secondly, stereodeficient subjects demonstrate a wide range of mHOKN asymmetries with some being symmetrical or nearly symmetrical (Mein, 1983; Demer and von Noorden, 1988; Hartmann *et al.*, 1993; Timms *et al.*, 1995). Thirdly, symmetrical mHOKN has been observed in the functioning eye of some infants who have no possible binocularity because of profound uniocular visual deprivation from birth (Day, 1995; Shawkat *et al.*, 1995). Finally, clinically obvious mHOKN asymmetry can occur in patients with congenital esotropia who are aligned early and develop high-grade stereopsis (Aiello *et al.*, 1994; Wright, 1996). These studies suggest, therefore, that the development of mHOKN symmetry and binocularity are separate processes and that the development of mHOKN symmetry may be affected by very early abnormal and possibly rivalrous vision from both eyes (Harris, 1997).

Recently, investigators looking at the effects of deprivation of normal binocular vision from birth in monkeys have suggested that a loss of binocularity in the NOT, rather than the visual cortex, cause mHOKN asymmetries. In monkeys reared with binocular lid suture for the first 25-55 days of life, in contrast to normal monkeys in whom all NOT units are sensitive to stimuli to either eye, the NOT becomes monocular, the majority of NOT units being dominated by the contralateral eye. It is suggested that asymmetries in mHOKN are due to this loss of binocular cells in the NOT because when the NOT loses its cortical input from the ipsilateral eye it responds only to T-N motion viewed from the contralateral eye (Tusa *et al.*, 2001; Mustari *et al.*, 2001; Tusa *et al.*, 2002). There was also a failure to develop binocular driving of neurons in the middle temporal (MT) visual area in one monkey reared with binocular lid suture (Tusa *et al.*, 2002). This finding has also been reported in monkeys surgically made esotropic early in life (Kiorpes *et al.*, 1996).

1.4.2 Development of vertical OKN

There has been little study of vertical OKN in infants, probably because it is difficult to stimulate, evaluate and record precisely. The results of the only published developmental study of vertical OKN indicated that infants show bi-ocular vertical OKN which has a lower beat frequency, a greater variability and a tendency for lower gain when the OKN stimulus moves downwards. By 4 months of age the responses to upward and downward stimulus motion were symmetrical but the slow phase gain of vertical OKN was still lower than in older children and adults. This study, however, used a small field display (subtending 30° horizontally and 22° vertically), and only one stimulus speed, a rather slow 7°/s (Hainline *et al.*, 1984a).

Vertical OKN responses in human subjects who have not had normal visual development have not been as well studied as horizontal responses. Asymmetries in the amblyopic and non-amblyopic eyes of some adult amblyopes, as well as in the deviating and non-deviating eyes of some strabismic subjects have been found (Schor and Levi, 1980; Proudlock *et al.*, 2001). In these patients upward stimulus movement presented monocularly elicited poor OKN while downward OKN remained robust. On the other hand, Tychsen *et al.* (1984) reported that patients with early onset strabismus show reductions of bi-ocular vertical OKN in response to downward stimulus motion, whereas clinically similar patients whose strabismus was of later onset do not show a marked vertical OKN asymmetry.

1.5 Abnormal OKN in clinical populations

OKN testing can be very useful to the clinician because OKN is a sensitive indicator of the condition of the oculomotor system and can be elicited even from the young infant. Assessment of optokinetic responses can be extremely helpful in the investigation of the apparently blind child since it can be used to distinguish between cortical blindness, saccade initiation failure ("ocular motor apraxia") and delayed visual maturation. OKN testing can also aid in determining the site of a brain lesion. It is important to recognise that both the slow and the quick phases are required for OKN, and that clinical disorders can affect them separately.

1.5.1 Complete absence of horizontal OKN

There are five main reasons for complete absence of bi-ocular horizontal OKN:

(1) *Grossly defective visual acuity.* A minimal amount of vision is necessary to elicit OKN (Pasik *et al.*, 1959) and in the case of total cortical blindness there is a prevalent conviction that OKN is absent (Velzeboer, 1952; Brindley *et al.*, 1969; Sadeh *et al.*, 1983; Aldrich *et al.*, 1987; Celesia *et al.*, 1991; Chatterjee and Southwood, 1995; Verhagen *et al.*, 1997). On the other hand, it is very difficult to suppress full-field OKN deliberately and if a subject with both eyes open views a stimulus of suitable speed that fills a substantial part of the visual field, OKN will occur involuntarily. Thus, a complete absence of OKN can indicate extremely poor vision.

(2) *A bilateral lesion of the horizontal optokinetic neural pathway.* Failure to elicit any horizontal OKN, when a subject with normal visual acuity views a large-field stimulus with both eyes open, may also be due to a *bilateral* lesion affecting the optokinetic neural pathway. This may involve the cortex, brainstem or cerebellum. If the OKNd pathway is intact some slow build-up OKN may still be present.

In our experience with infants and children, if the lesion involves the cortex there is no spontaneous nystagmus in any position of gaze and no fixing or following can be elicited. With lesions of the brainstem and cerebellum other oculomotor signs are usually present to aid in determining the site of the lesion (see Appendix).

(3) *Lack of ocular movement.* Bi-ocular horizontal OKN may also be absent due to a lack of ocular movement – that is, a gaze paresis. The doll's head manoeuvre, however, can be used to determine whether there is indeed a complete absence of eye movement.

(4) *Horizontal 'congenital nystagmus' (CN).* Horizontal CN, whether it be due to a sensory defect or of idiopathic origin, is usually associated with complete failure of horizontal OKN. When patients with horizontal CN are presented with a horizontally moving optokinetic stimulus, the spontaneous nystagmus will usually continue unabated but there may be a shift in the null zone position of the spontaneous nystagmus. If this 'null-shifting' occurs when the stimulus field moves from left to right, the right-gaze nystagmus (usually right beating) is observed in the primary position and, if the field moves from right to left, the left-gaze nystagmus becomes apparent (Halmagyi *et al.*, 1980; Abadi *et al.*, 1982). Occasionally CN may be completely suppressed by a horizontally moving optokinetic stimulus, still without OKN (Harris, 1997b).

In contrast, patients with some types of acquired nystagmus may show OKN with their own nystagmus superimposed on the OKN slow phases (Harris, 1997a).

(5) *Saccade initiation failure (SIF) ("ocular motor apraxia").* SIF is a term used to describe an inability to execute saccades. This includes an intermittent delay or failure in the triggering of OKN quick phases which, in all affected patients during bi-ocular OKN testing, will intermittently allow the eyes to become deviated to the mechanical limit of gaze (Cogan, 1972; Harris *et al.*, 1996b). This phenomenon has been called 'lock-up' and does not occur in healthy infants over 1 month of age (Harris, 1997b).

Head thrusting to shift gaze is a manoeuvre adopted by many children to compensate for their saccade deficit. The detection of head thrusting has traditionally been used for the identification of cases of SIF. However, it may not always be adopted and, in older children, it may be superseded by a strategy in which triggering of saccades is facilitated by blinking at the same time as the saccade (synkinetic

blinking) (Zee *et al.*, 1983). However, as normal adults may also blink synkinetically, recognition of synkinetic blinking does not always help in the diagnosis of SIF. We consider that, instead of looking for these compensatory behaviours, a more reliable test for SIF is to examine the quick phases of induced OKN.

SIF can occur in the horizontal or vertical plane (see 1.5.5) and may be congenital or acquired. Although frequently found to be idiopathic, SIF has been associated with a wide range of conditions (Harris, 1997b). A surprising number of patients with SIF, including idiopaths, also have motor and speech delay (Fielder *et al.*, 1986; McCarry *et al.*, 1987; Rowe, 1995; Harris *et al.*, 1996b).

1.5.2 Bi-ocular horizontal OKN asymmetries

A *unilateral* lesion of the horizontal optokinetic neural pathway will result in an asymmetry of bi-ocular horizontal OKN. The amplitude, slow phase velocity and beat frequency of bi-ocular horizontal OKN induced by a stimulus moving towards the damaged side of the brain will be reduced compared with the horizontal OKN induced by a stimulus moving towards the undamaged side. When there is no nystagmus present, this bi-ocular horizontal OKN asymmetry is often localising to the parietal lobe (Baloh *et al.*, 1977). This may or may not be associated with an ipsilateral homonymous hemianopia (Baloh *et al.*, 1980b). Isolated bi-ocular horizontal OKN asymmetry has been reported in infants as young as 4-5 months (Braddick *et al.*, 1992; Jacobs *et al.*, 1993).

Patients with acute unilateral peripheral vestibular lesions, that is lesions of the labyrinths and/or vestibular nerves, may also have asymmetrical bi-ocular horizontal OKN. In such cases there is an increased slow phase velocity towards the side of the lesion, i.e. in the direction of their spontaneous nystagmus (Ciuffreda and Tannen,

1995). However, once compensation occurs, this horizontal OKN asymmetry disappears within a few days.

When horizontal OKN is tested with both eyes open and if the vision in one eye is severely reduced, any existing mHOKN asymmetry will be revealed and may give the impression of a bi-ocular OKN asymmetry. Care must be taken, therefore, in interpreting the results of OKN tested with both eyes open.

1.5.3 Monocular horizontal OKN asymmetries

As discussed above (see 1.4.1) in normal infants, and in human subjects who have had normal visual development interrupted early in life, mHOKN is asymmetrical. Asymmetries of mHOKN and slow build-up OKN, have also been noted in patients with rod monochromatism (Baloh *et al.*, 1980a). The slow build-up was found to be more prominent in the T-N direction than in the opposite direction.

1.5.4 Delayed visual maturation

Delayed visual maturation (DVM) is a condition characterised by visual unresponsiveness in early infancy which spontaneously improves, often to normal levels, by 4-6 months of age (Tresidder *et al.*, 1990). Harris and colleagues (Harris *et al.*, 1996a) studied the optokinetic responses of six DVM infants (aged 2-4 months) who were still at the stage of complete visual unresponsiveness. No saccades or tracking, with either the eyes or the head, to visual objects could be elicited. Remarkably, a normal full-field rapid build-up horizontal OKN response was recorded when viewing bi-ocularly or during monocular stimulation in the T-N direction of the viewing eye. However, almost no mHOKN could be elicited during

stimulation in the N-T direction, which was significantly poorer than the age-matched infants. Pattern visually evoked potentials (VEPs) were of normal amplitude and latency for the age of the patient. Thus, although this study included only a small sample, it suggests that the demonstration of OKN and normal pattern VEPs in an otherwise visually unresponsive infant indicates that, in the absence of other neurological problems, the visual outcome will probably be very good.

It is important to note that the stimulus employed by Harris and colleagues filled the entire visual field. If a hand-held OKN drum or tape were used as a stimulus when testing the DVM infant a response would probably not be elicited (Cole *et al.*, 1984).

1.5.5 Abnormalities of vertical OKN

As mentioned previously vertical OKN has not been as extensively investigated as horizontal OKN and thus abnormalities of this response are not as well understood. Abnormal vertical OKN responses have been reported in patients with strabismus and patients with amblyopia (see 1.4.2). Absent bi-ocular vertical OKN, in either direction or both, has been associated with lesions of the midbrain (Jacobs *et al.*, 1973; Büttner-Ennever *et al.*, 1982; Siatkowski *et al.*, 1993).

SIF can also occur in the vertical plane. This is unusual and can indicate neurometabolic diseases such as Niemann-Pick Type C (Sanders and Wybar, 1969; Neville *et al.*, 1973), in which it may be the presenting sign (Shawkat *et al.*, 1994), or Gaucher disease (types 2 and 3) (Vivian *et al.*, 1993; Harris *et al.*, 1997) or a midbrain lesion (Ebner *et al.*, 1990).

1.6 Aims

We believe that OKN is undervalued as a clinical tool. In this thesis we will investigate how both the slow and the quick phases of horizontal and vertical OKN may have a role in the assessment of the oculomotor system.

Eliciting sufficient saccades from infants and children in order to draw conclusions about their speed is very difficult. OKN quick phases are thought to be essentially saccadic in nature. Thus, if it could be shown that saccades and OKN quick phases share the same temporal characteristics and are affected by the same disease processes it should be feasible to assess OKN quick phases as a substitute for measuring saccades. To determine this, in Chapter 3 of this thesis, we will compare horizontal saccades with horizontal OKN quick phases (and in Chapter 6 we will compare vertical saccades with vertical OKN quick phases). Further, in Chapter 4, we will look at the temporal characteristics of horizontal OKN quick phases in normal infants. We will also examine horizontal OKN quick phases in a group of children with Gaucher disease. This disease is known to be associated with slow saccades.

The quick phases of full-field horizontal OKN not only reset the eyes but also moved them in the opposite direction to stimulus movement (we will refer to this as "contraversion"). It has been suggested that this response is a strategy for directing the line of sight into the visual field from which motion is originating. The aim of Chapter 5 will be to define more clearly this phenomenon and, based on a detailed study of a patient in whom this response was excessive, propose an alternative explanation for the occurrence of contraversion.

Clinical assessment of eye movement disorders often includes examination of horizontal OKN but vertical OKN is rarely examined. Since the anatomical pathways controlling horizontal and vertical OKN differ in some respects, lesions and disease

processes may affect only one direction. Therefore, to the clinician it may be just as important to test vertical OKN as it is to test horizontal OKN. However, before studying vertical OKN in the clinical setting it is necessary to establish the dynamics of the response in normal subjects. Thus, in Chapter 6 we will examine vertical OKN in normal adult subjects.

In Chapter 7 we will describe how we tested vertical OKN in infants and children referred to the Eye Movement Laboratory at Great Ormond Street Hospital. This was to determine whether, when identifying neurological disorders, it is useful to assess vertical OKN in addition to horizontal OKN.

It is well established that abnormal visual experience early in life can lead to abnormal horizontal OKN. Thus, it is necessary to establish whether vertical OKN is also abnormal in such patients. Therefore, in Chapter 7, we will assess the optokinetic responses of a group of patients who, from childhood, have had misalignment of their visual axis.

Chapter 2 - Methodology

2.1 Introduction

The experiments in Chapters 3, 4 and 5 and the first experiment of Chapter 7 were carried out at the Eye Movement Laboratory at Great Ormond Street Hospital, London, UK. This laboratory was designed for the clinical assessment of infants and children. All other experiments were conducted in the Ocular Motor Neurophysiology Laboratory at the Department of Veterans Affairs Medical Center, Case Western Reserve University, Cleveland, USA.

Three techniques were used for recording eye movements: electro-oculography, infrared limbal reflection and the magnetic search coil. In this chapter we will describe these recording techniques, the stimuli used to elicit OKN and our analysis program.

2.2 Visual stimuli

2.2.1 Horizontal OKN

A brightly coloured curtain was used to elicit horizontal OKN in the experiments described in Chapters 3, 4 and 5. The curtain was covered with high contrast pictures of animals and other attractive shapes of various spatial frequencies. This was illuminated at ordinary room levels. The curtain was 175 cm high and completely surrounded the subject or the parent and infant to form a cylinder of a radius of 75 cm. The stimulus covered the full horizontal visual field and 100° of the vertical visual field. Older subjects sat alone in a Bárány chair, younger children sat

on a parent's lap. The head was supported by a chin rest, or held by the parent (Figure 2.1a).

The subjects were monitored at all times by a video camera. The video image and eye movement signals were relayed to the adjacent room for recording (Figure 2.1b). The eye movement signal was superimposed upon the video image allowing the eye movement trace and the visual appearance of the eyes to be examined together (Jacobs *et al.*, 1992; Harris *et al.*, 1992). The comments of the two operators and the vocalisations of the subject were also recorded simultaneously with the recording of the eye movement signal.

a

b

Figure 2.1. The horizontal OKN stimulus

(a) The horizontal optokinetic stimulus was a brightly coloured curtain. Older subjects sat alone, infants sat on a parent's lap and their head was gently restrained.

(b) The infants were monitored by video at all times and the video image and EOG signal were relayed to the adjacent room for superimposition and recording.

2.2.2 Vertical OKN

Horizontal black and white stripes, rear-projected onto a semi-translucent screen, were used to elicit OKN in the experiments discussed in Chapter 6 and 7. Details of the size of the screen, spatial frequency and speed of the stimulus are given in the methodology section of the relevant chapter.

The stimuli were generated by a Cambridge Research Systems VSG2/5 visual stimulus generator and projected using an Epson Powerlite 9100i video projector (Chapter 6 and second experiment of Chapter 7) or a Barcodata 808 video projector (first experiment of Chapter 7). The room lights were extinguished during testing and all ambient light came from the projector.

Figure 2.2 The vertical OKN stimulus used in Chapter 6 and the second experiment of Chapter 7

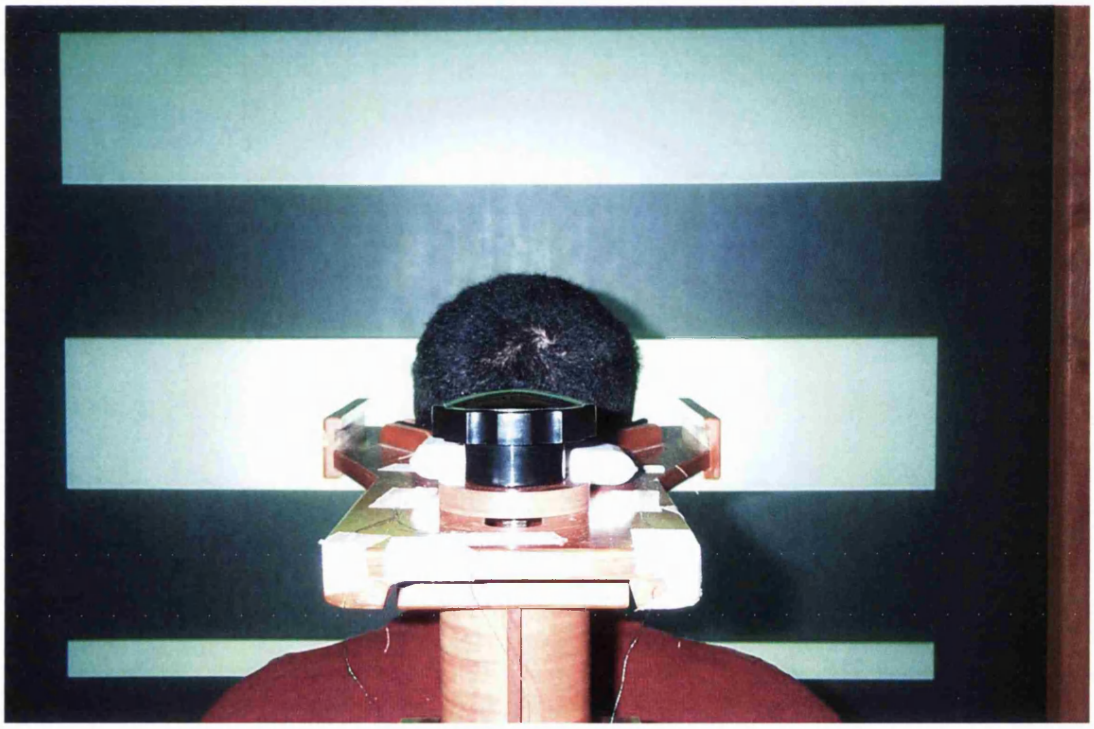


Figure 2.3 The vertical OKN stimulus used in the first experiment of Chapter 7

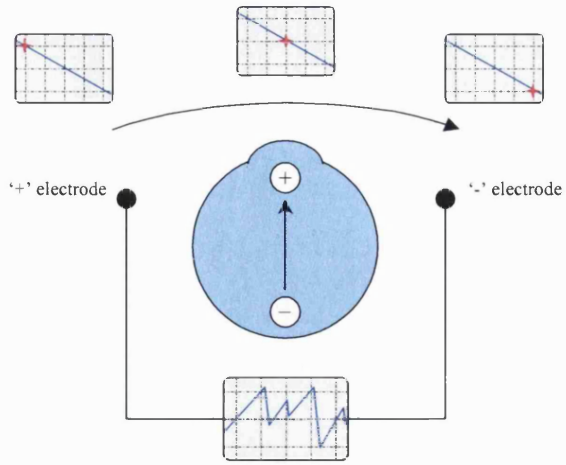
2.2 Eye movement recording

It has previously been shown that OKN is not affected by mild retinal blurring (Dichgans, 1977; Post *et al.*, 1979). Therefore, unless the subjects wore contact lenses, they were recorded without refractive correction as glasses frames could limit the extent of the visual field.

2.2.1 Electro-oculography

Electro-oculography (EOG) is based on the premise of the eyeball being an electric dipole, with the cornea being more positive than the posterior pole of the eye. EOG measures the position of the eye by sensing the corneo-retinal potential. To do this, surface recording electrodes are attached to the outer canthi to record horizontal movements, and above and below one eye to record vertical eye movements.

Figure 2.4 The principle of electro-oculography



EOG has a resolution of 1 to 2° (Young and Sheena, 1975) and, although it may not be ideal if high resolution of eye movements is required, in the clinical setting it has a number of advantages over other recording techniques. It is the simplest and cheapest method and can measure the full oculomotor range. EOG does not require any cumbersome equipment attached to the head or before the eyes and, therefore, there are no limitations to the subject's field of vision. A further advantage of EOG is that it can record eye movements even under closed lids (e.g. in cases of ptosis). However, EOG does suffer from a number of limitations including occasional drifting of the corneo-retinal potential, changes of the corneo-retinal potential with ambient light level, contamination of eye movement recordings by potentials from facial and eyelid muscles and limited bandwidth due to the filtering required to remove noise from the signal (Leigh and Zee, 1999).

Bi-temporal DC-coupled EOG was used to record horizontal eye movements in the experiments discussed in Chapters 3, 4 and 5 of this thesis. Self-adhesive silver/silver chloride electrodes were placed at the outer canthus of each eye and a common mode reference electrode was sited at the mid-forehead. Rubbing the skin

with alcohol and a mild abrasive cream prior to electrode application ensured good contact.

The eye movement signal was sampled at 1090 Hz and the electrodes were DC-coupled to an isolated amplifier with switchable low-pass zero-phase Bessel filters (bandwidth 0-30 Hz). The filtered signal was recorded on an eight-channel digital audio tape (DAT) recorder (Biologic DTR-1800) and was also monitored in real-time on an oscilloscope. The DAT converts the analogue input to a digital signal with 14-bit precision and stores it on digital tape. Other channels of the recorder were allocated to the infrared eye tracker, the optokinetic curtain tachometer and to the output of a photodiode that sensed the level of room illumination (Jacobs *et al.*, 1992).

2.2.2 Infrared limbus eye tracker

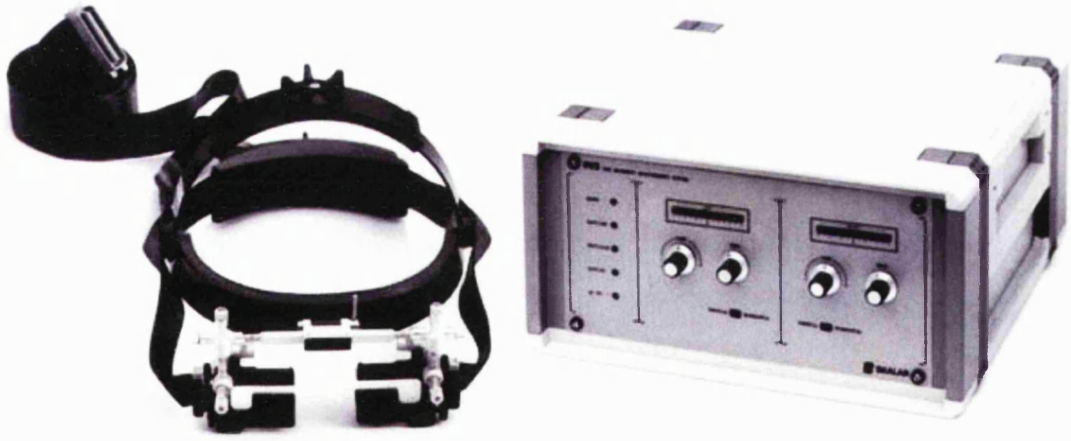
Although EOG is the most suitable method for assessing the eye movements of infants and children it is not suitable for more accurate eye movement research. Therefore, an infrared limbus eye tracker was used simultaneously with EOG in the experiments discussed in Chapters 3 and 5. In this technique the eye is diffusely illuminated with infrared light, which is differentially reflected by the iris and sclera back to photo-transistors positioned near the lower limbus. The photo-transistors transform the reflected infrared light into a voltage. The voltage of the nasally located photo-transistors is subtracted from the voltage of the temporally located photo-transistors and the resulting voltage is proportional to the angular deviation of the eye.

We used an IRIS eye tracker (Skalar Medical, Delft, The Netherlands. Model 6500). This system consists of two infrared light transducers, one before each eye, attached to a light-weight helmet (Figure 2.5). The transducers can be positioned to record horizontal or vertical eye movements but, in this thesis, only horizontal

movements were recorded using the eye tracker. The transducers do not obstruct the horizontal visual field. The system had a horizontal recording range of ±30° although 97% linearity was only guaranteed within ±25°. The optimal resolution of this system is 2 min arc (0.03°).

The infrared light transducers were made up of an array of nine infrared light emitting diodes (LED) and nine infrared light sensitive photo-transistors. The detector array was positioned below the LED array. For optimal alignment both transducers could be adjusted independently in three mutually perpendicular directions. The eye tracker connecting cables were screened with copper tape to reduce pick-up from surrounding electronic devices.

Figure 2.5. The IRIS infrared eye tracker.



Eye movements recorded using the eye tracker were sampled at 1090 Hz and then stored on DAT on a channel of the recorder described above. These eye position data were then filtered using a zero-phase low-pass digital filter (bandwidth 0-64 Hz). Only data recorded from the left eye was analysed.

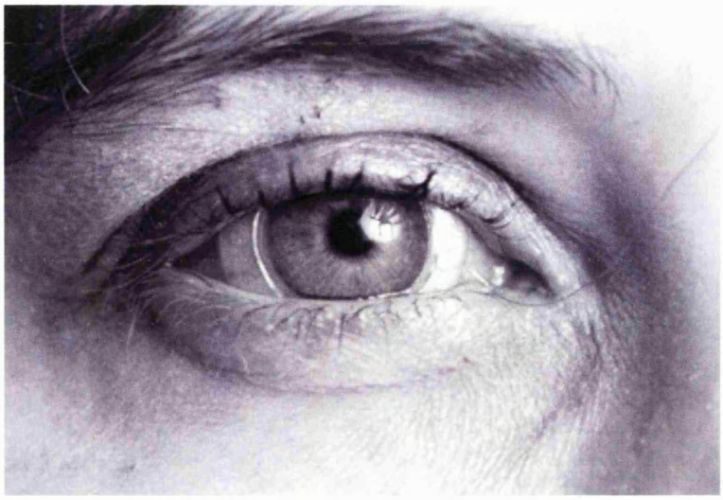
2.2.3 Magnetic search coil technique

The magnetic search coil technique is the most reliable method for recording vertical eye movements and so was the technique chosen for the experiments described in Chapters 6 and 7. In this method, two orthogonal pairs of field coils surround the subject and induce voltage changes in fine coils embedded in a soft annular contact lens worn by the subject. These voltage changes are related to horizontal and vertical eye position.

We used a magnetic search coil system (CNC Engineering, Seattle, WA) that had 6-foot field coils. This system used a rotating magnetic field in the horizontal plane and an alternating magnetic field in the vertical plane. Using a protractor device the search coils were calibrated before each experimental session. The system was 98.5% linear over an operating range of ± 20° in both planes. Crosstalk between vertical and horizontal channels was less than 2.5% and the standard deviation of system noise was less than 1.2 min arc (0.02°). Subjects were required to wear a silastic annulus (Figure 2.6) on one or both eyes and topical anaesthetic drops (Proparacaine HCL 0.5%) were administered prior to insertion of the annulus. All experimental sessions lasted less than thirty minutes, a period that was found to be well tolerated.

The coil signals were sampled at 500 Hz with 16-bit resolution after passing through Butterworth filters (bandwidth 0-150 Hz). These digitised coil signals were then passed through an 80-point Remez FIR (bandwidth 0-140 Hz).

Figure 2.6. Subject wearing a silastic annulus.



Subjects were required to wear a silastic annulus on one or both eyes in which are imbedded coils of fine wire. A wire from the annulus leaves the eye at the nasal canthus.

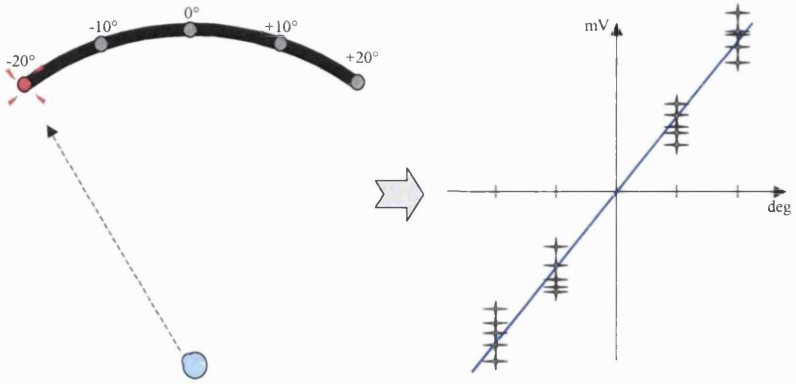
2.3 Calibration

Calibration was performed before each experimental session. Unless otherwise stated, the calibration procedure for EOG and the infrared eye tracker was as follows. A calibration array, on a black horizontal stimulus arc, was placed at eye level 100 cm in front of the subject. Target points (red LEDs) were located at equal intervals (10°) from 20° right to 20° left with respect to the subject's midsagittal plane and were illuminated in a pseudo-random order. The subject was instructed to fix on the target points while keeping his head still and aligned with the central target.

The change in voltage corresponding to each saccade was measured interactively by placing a cursor at the beginning and end. We then plotted eye position (in volts) against angular target position (in degrees). A regression line fitted to this plot allowed a conversion of the recorded signal from volts into degrees. The regression was constrained to pass through the origin because no eye movement corresponds to no change in voltage. The reciprocal of the regression slope for each

session was used as the calibration factor for converting voltage to degrees of eye movement for that session.

Figure 2.7 The calibration principle



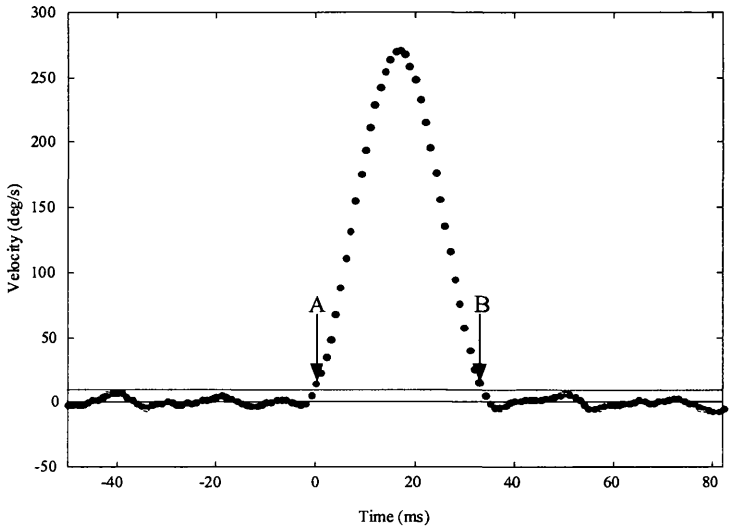
During the calibration procedure the subject viewed five red LEDs one located in the centre and the others at 10° intervals from 20° right to 20° left. The LEDs were illuminated in a pseudo-random order. The change in voltage corresponding to each saccade was then plotted against target position. A regression line fitted to this plot allowed a conversion of the recorded signal from volts into degrees.

2.4 Analysis program

The filtered eye position data was differentiated to give the eye velocity data. All measurements were checked interactively and eye movements associated with blinks were rejected. Eye movements to the right were examined independently from those to the left. Our standard computer program, implemented in MATLAB, was used to determine the characteristics of the eye movements. Firstly, the program picked out all the saccades and OKN quick phases (fast eye movements, FEMs). A FEM was detected when the velocity was continuously above 100°/s for at least five points. This high threshold was chosen to avoid accidental detection of slow phases. The peak velocity of each FEM was then determined. FEM onset and offset were then defined as the last points either side of the peak velocity before which the velocity fell

below 10°/s. These points were used to calculate the amplitude and duration of the FEMs (Figure 2.8).

Figure 2.8. Schematic diagram of a typical saccade



The diagram illustrates the points picked out by the computer program as the beginning (A) and end (B) of the fast eye movement. Blue line indicates the 10°/s threshold. Each red dot represents a sample point.

We also examined the slow phases of OKN. The start and end points of the slow phases were defined according to a $0°/s^2$ acceleration threshold (in order to obtain acceleration data differentiation was performed on the velocity data). This was to avoid any possible overlap with the OKN quick phases. The velocity of each slow phase was calculated from the mean of its instantaneous velocities. At each stimulus speed, the OKN gains were calculated by averaging (mean) over *all* the slow phases after any that were associated with blinks or head movements had been removed.

The data was imported into SPSS (v10.1 for Windows) and all statistical analyses were performed using this software package.

Chapter 3 - Comparison of Horizontal Saccades and OKN Quick Phases

3.1 Introduction

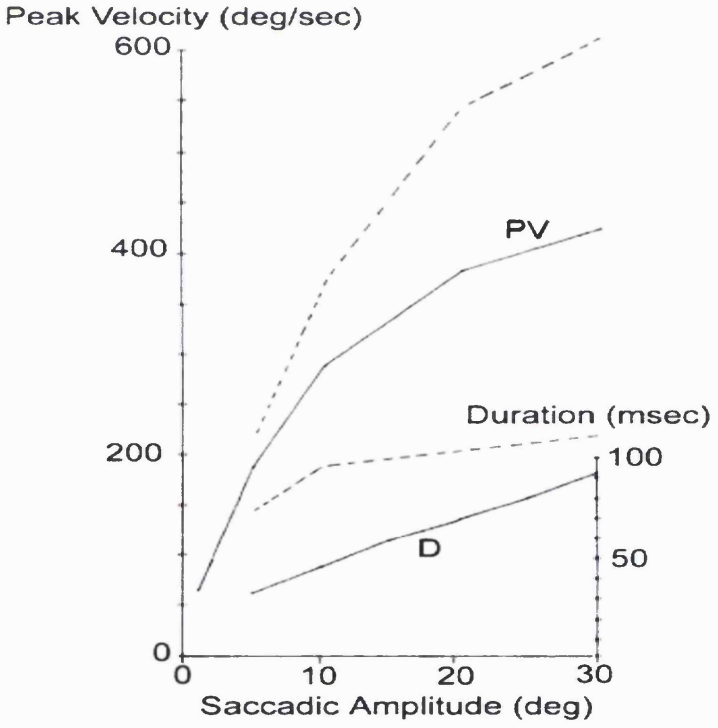
Abnormalities in the saccadic main sequence are an important finding and may indicate pathology of the oculomotor periphery or central neurological disorders. However, in young or unco-operative patients it can be difficult eliciting a sufficient number of saccades to measure the main sequence. It has been suggested that the quick phases of OKN are identical to saccades. If indeed this proves to be the case it would be feasible to use OKN, an involuntary response that is easily evoked, as a simple way of eliciting many saccades.

Clinical and neurophysiological studies have indicated that horizontal saccades and the quick phases of horizontal optokinetic and vestibular nystagmus have the same anatomical substrate in the paramedian pontine reticular formation (PPRF) (Bender and Shanzer, 1964; Cohen and Feldman, 1968; Cohen and Komatsuzaki, 1972; Cohen and Henn, 1972; Keller, 1974). Therefore, a priori, it seems plausible that saccades and quick phases should have similar speeds, and that a disease process causing a slowing of saccades should also lead to slowing of quick phases. Amplitude, duration and peak velocity are three of the main parameters used to describe saccades. Thus, for OKN quick phases to be the same as saccades these temporal characteristics should also be the same.

3.1.1 The main sequence for horizontal saccades

Both the duration and peak velocity of saccades can be characterised by their stereotypical relation with respect to saccade amplitude. This relationship is known as the main sequence (Boghen *et al.*, 1974; Bahill *et al.*, 1975). For saccades above approximately 4°, duration increases linearly with amplitude. Linearity is lost at the larger amplitude end of the spectrum at around 50°. Peak velocity also increases with amplitude but there is a progressive saturation beyond amplitudes of 20°, with asymptotic values of about 500°/s (Leigh and Zee, 1999). Unlike the relationship between duration and amplitude, that between peak velocity and amplitude is non-linear but follows a logarithmic law (Zuber and Stark, 1965; Bahill *et al.*, 1975).

Figure 3.1. The main sequence relationship for saccades



The main sequence for duration (D) and for peak velocity (PV). Dashed lines indicate one standard deviation of velocity. From Leigh and Zee, 1999.

3.1.2 Previous studies comparing saccades and nystagmus quick phases

A number of investigators have compared the main sequences for duration and/or peak velocity of horizontal saccades with the quick phases of OKN or the quick phases of vestibular nystagmus (VN). Some degree of similarity has been shown although inconsistencies have also been reported.

3.1.2.1 Animal studies

Ron *et al.* (1972) compared spontaneous saccades with VN quick phases, in five monkeys. VN was induced by rotation, electrical stimulation of the vestibular nuclei, injection of potassium chloride into the flocculus and also by caloric irrigation. These eye movements were recorded using a magnetic search coil and were studied in a structured visual field, in total darkness and with an illuminated ganzfeld. The investigators concluded that the main sequence for duration of spontaneous saccades and quick phases induced by rotation were very similar up to 25°. For larger movements quick phases were slightly *faster* than saccades. Visual field structure, illumination and darkness affected the duration of both types of FEM similarly. On the other hand, quick phases that were induced by electrical stimulation, potassium chloride injection or caloric stimulation were quite different. The duration of these quick phases was increased by a factor of two or three compared to rotatory quick phases and saccades.

In three cats, Guitton and Mandi (1980) compared the main sequences for duration and peak velocity of spontaneous saccades with the quick phases of VN induced by sinusoidal rotation. These investigators also measured eye movements

using surgically implanted magnetic search coils and assessed them in the light and in the dark. They found that despite considerable variability, it appeared that the temporal characteristics of saccades and these VN quick phases were the same.

3.1.2.2 Human studies

In humans, despite a number of studies comparing horizontal voluntary saccades with the quick phases of OKN and/or the quick phases of VN, there is no consensus as to whether these FEMs share the same temporal characteristics.

Voluntary saccades compared to OKN quick phases

Four studies have concluded that voluntary saccades, elicited to fixed targets in the light, are similar to OKN quick phases (Mackensen and Schumacher, 1960; Dichgans *et al.*, 1973; Sharpe *et al.*, 1975; Jürgens *et al.*, 1981a).

Mackensen and Schumacher (1960) were the first to compare saccades and OKN quick phases. Using bi-temporal EOG, they concluded that the main sequences for duration and peak velocity were the same. However, they measured the OKN quick phases in only two subjects (themselves) and compared them to saccades not recorded at the time but reported in two previous papers (Westheimer, 1954; Mackensen, 1958).

In four human subjects, Dichgans *et al.* (1973) used EOG to compare the peak velocities of voluntary saccades with OKN quick phases. They found that voluntary saccades were slightly faster than OKN quick phases of identical amplitudes. However, statistically, the saccades were significantly faster than OKN quick phases only at amplitudes greater than 20° and only to the left.

Sharpe *et al.* (1975) tested ten human subjects using the more accurate measurement technique of infrared reflection. These investigators agreed with Dichgans and co-workers and Mackensen and Schumacher that the main sequence for peak velocity of voluntary saccades and the quick phases of OKN were the same. However, they used an OKN stimulus with a velocity varying between 3 and 10°/s and instructed their subjects to stare straight ahead and note each stimulus stripe. At these low stimulus speeds and with these instructions, the induced 'optokinetic' quick phases would be more like voluntary saccades.

Jürgens *et al.* (1981a), using bi-temporal EOG, compared the durations of voluntary saccades and OKN quick phases. They found that for a given amplitude quick phases of OKN have "about the same" duration as saccades, but these were only preliminary results.

In contrast to these four experiments, where similarities between the temporal characteristics of horizontal OKN quick phases and saccades were found, Henriksson *et al.* (1980) and Gavilán and Gavilán (1984) found that saccades were significantly faster than OKN quick phases. Both groups of investigators used bi-temporal EOG and measured the velocity of these FEMs (peak velocity was measured by Henriksson *et al.*, average velocity was measured by Gavilán and Gavilán). Henriksson *et al.* compared OKN quick phases to saccades made in the light but Gavilán and Gavilán (1984) measured saccades in the dark.

Voluntary saccades compared to VN quick phases

In the majority of the experiments above, the quick phases of VN were also assessed and compared to voluntary saccades. Again opinion as to whether these FEMs are the same is divided.

Dichgans *et al.* (1973) and Sharpe *et al.* (1975) felt that voluntary saccades and the quick phases of VN shared the same main sequences for peak velocity. In Dichgans and co-workers' experiment, VN was induced by rotation, firstly with the eyes open under high plus Frenzel's glasses (to exclude fixation) and secondly with the eyes closed. With the eyes closed the quick phases of VN corresponded to voluntary saccades initiated under the same conditions. With Frenzel's glasses they corresponded to voluntary saccades in a homogeneously illuminated visual field. Sharpe *et al.* elicited VN by caloric stimulation and also by rotation. In the light there was no significant difference between the peak velocities of saccades and VN quick phases and both were found to slow similarly in darkness.

Three experiments concluded that voluntary saccades and the quick phases of VN were significantly different (Henriksson *et al.*, 1980; Jürgens *et al.*, 1981a; Gavilán and Gavilán, 1984). Henriksson *et al.* (1980) assessed voluntary saccades in the light, in the dark and behind closed lids. VN was induced by caloric stimulation and by rotation, both of which were in darkness. These workers concluded that, at the same amplitude and during the same visual conditions, the saccades had a significantly higher peak velocity than the quick phases of VN. Jürgens *et al.* (1981a) found that voluntary saccades made either in the light or in the dark were clearly faster than the quick phases of VN elicited by sinusoidal rotation in the dark. Gavilán and Gavilán (1984) compared the average velocity of voluntary saccades with VN quick phases (caloric and rotational). Both saccades and VN were measured in the dark. These investigators found that for the same amplitude of movement the velocity of the saccades were considerably greater than the quick phases of VN.

Thus, although many investigators have compared saccades to nystagmus quick phases, there is still no agreement as to whether these FEMs share the same

temporal characteristics (see Table 3.1). These discrepancies may reflect methodological differences. Some investigators measured only duration, others measured only velocity (peak velocity or average velocity) and some measured both. Also the studies elicited the quick phases of nystagmus and voluntary saccades under different conditions (light and/or dark; eyes open/eyes closed). Further, different recording techniques and signal processing may have lead to different conclusions.

In this study we re-examine this issue because our ultimate aim is to be able to use the main sequence for OKN quick phases to approximate the main sequence for saccades. We compared the main sequences for duration and for peak velocity of horizontal reflexive saccades with those of OKN quick phases. These FEMs were elicited from normal adult subjects in the light. OKN was chosen over VN since it can be easily elicited from the newborn (Dayton and Jones, 1964; Kremenitzer *et al.*, 1979; Schor *et al.*, 1983) and if whole field stimulation is used it is virtually impossible to suppress. On the other hand, in our clinical experience, VN can be very variable in the young infant.

In this study we also compared two eye movement recording techniques; infrared limbal reflection (IR) and EOG. IR was chosen because it is very accurate. However, it is cumbersome and of limited value in the paediatric clinical setting. In our paediatric eye movement laboratory we routinely use EOG. This is clinically practical for patients of all ages but not as accurate as IR. Before we could consider recording the main sequence of OKN quick phases from infants and children (see following chapter) we felt that it was necessary to determine that both IR and EOG yield similar results. Further, as discussed above, some investigators have reached different conclusions regarding whether saccades and quick phases are the same in

humans. Since these discrepancies could be explained by the choice of recording technique, we felt that by using IR and EOG simultaneously we controlled for this variable.

Table 3.1. Previous studies comparing the temporal characteristics of horizontal saccades and nystagmus quick phases

Author	Year	Method	Subjects	Saccades	OKN	VN	Measure	Conclusions
Ron et al.	1972	Magnetic search coil	5 monkeys	Spontaneous. Light/dark/ ganzfeld.	No	Rotational, caloric, electrical, chemical. Light/dark/ ganzfeld.	D	Saccades & rotational VN QPs same to 25° Similarly affected by visual field structure, dark & illumination. QPs of artificially induced VN longer duration.
Guitton and Mandi	1980	Magnetic search coil	3 cats	Spontaneous. Light/dark.	No	Rotational. Light/dark.	D PV	VN QPs and saccades - no significant difference in light or dark.
Mackensen and Schumacher	1960	EOG	2 adult humans	Voluntary.	Yes	Rotational.	D PV	OKN QPs and saccades - no significant difference.
Dichgans et al.	1973	EOG	4 adult humans	Voluntary. Up to 20 °.	Yes	Rotational	PV	OKN QPs lower PV than saccades but only significant at greater amplitudes and to left. VN QPs markedly slower.
Sharpe et al.	1975	Infrared reflection	10 adult humans	Voluntary. Light/dark. 1-10 °.	Yes 3-10°/s	Post-rotational, Caloric. Light/dark.	D PV	OKN QPs, VN QPs and saccades - no significant difference. Similarly affected by dark & illumination.
Jürgens et al.	1981a	EOG	Adult humans	Voluntary. Light/ dark (elicited acoustically). Up to 40 °.	Yes	Rotation in dark	D	OKN QPs and saccades in light about the same (preliminary results). VN QPs longer duration.
Henriksson et al.	1980	EOG	20 adult humans	Voluntary. Light/dark/ closed lids. 5-60 °.	Yes 90°/s	Per- and post-rotation, caloric in dark.	PV	OKN QPs and VN QPs lower PV than saccades. PV of OKN QPs = PV of VN QPs.
Gavilán and Gavilán	1984	EOG	57 adult humans (3 groups)	Voluntary. 5-40 °.	Yes 30, 60°/s.	Caloric in dark	AveV	AveV saccades>OKN QPs>VN QPs.

EOG: electro-oculography; A: amplitude; D: duration; PV: peak velocity; AveV: average velocity; VN: vestibular nystagmus; OKN: optokinetic nystagmus; QPs: quick phases.

3.2 Methodology

3.2.1 Subjects and recording methods

Ten healthy adult subjects were recorded (four male, six female). Their ages ranged between 25 and 48 years. None had a history of strabismus or had any known neurological or oculomotor problems.

Bi-ocular horizontal eye movements were measured using IR and bi-temporal DC EOG simultaneously. Subjects' heads were supported by a chin rest and the importance of keeping their heads still was stressed. Alertness was maintained by frequent verbal encouragement. Subjects were randomly assigned as to whether they had horizontal OKN or reflexive horizontal saccades tested first.

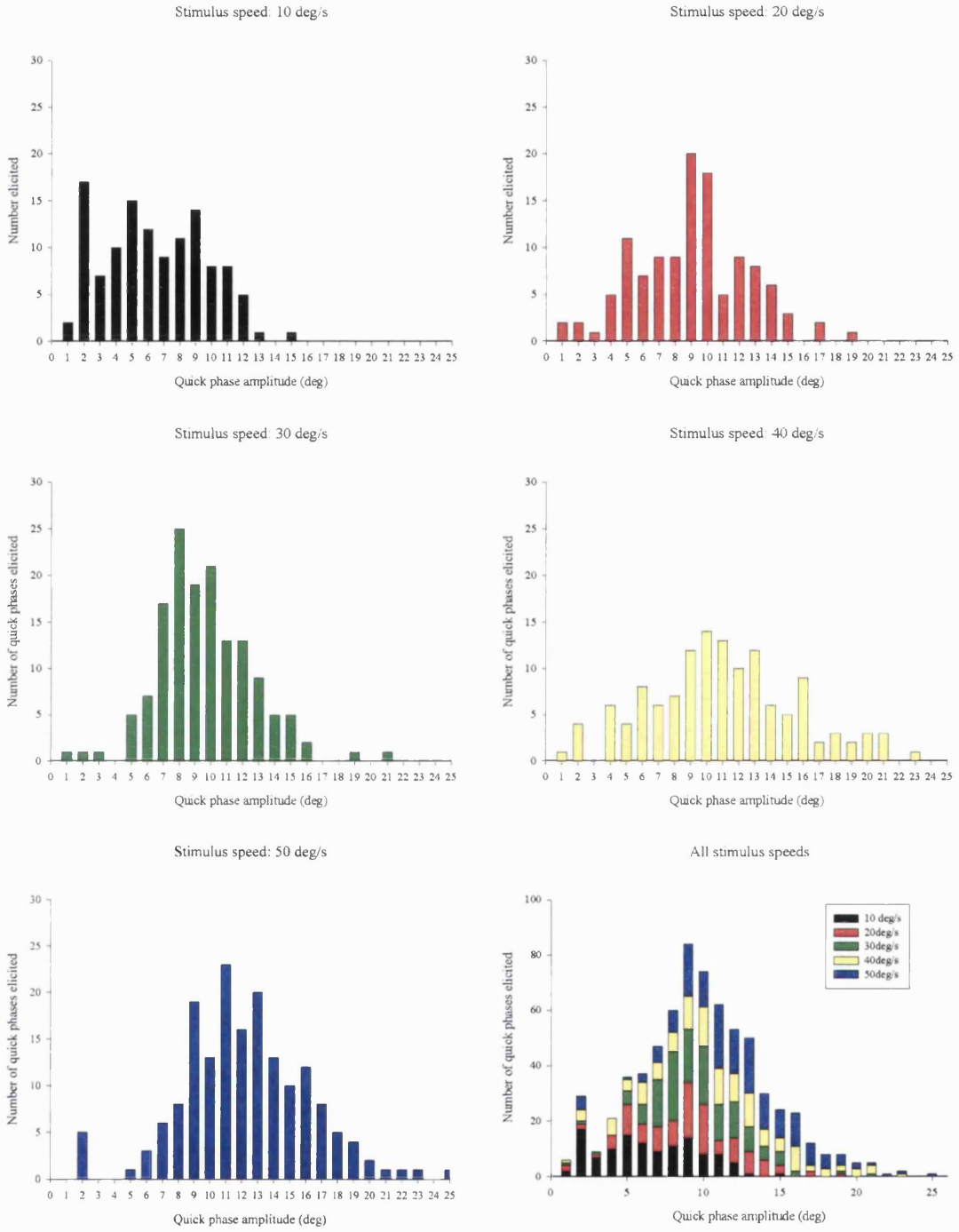
3.2.2 Visual stimuli

A full-field, brightly coloured, richly patterned curtain was used as the horizontal optokinetic stimulus (see Chapter 2). This was rotated around the subject for a total time of 5 minutes. The curtain was rotated rightward and leftward at speeds of 10, 20, 30, 40 and 50°/s for periods of 30 seconds each. The direction and speed of the stimulus were randomised. Preliminary experiments demonstrated that this range of stimulus speeds produced quick phases with a sufficient range of amplitudes to determine a main sequence, while ensuring that quick phase amplitudes were within the measurement range of the infrared eye tracker (Figure 3.2). Subjects were instructed to look straight ahead, to keep the curtain as clear as possible and not to track any individual feature. OKN quick phases not only reset the eyes but also move the eyes in the opposite direction to stimulus movement ("contraversion", see

Chapter 5). Thus, the OKN quick phases are essentially centrifugal eye movements. Contraversion could result in the quick phases being outside the measurement range of the infrared eye tracker. To avoid this, when excessive contraversion did occur, subjects were instructed to move their eyes to the centre.

The stimulus for eliciting reflexive saccades consisted of five red light emitting diode (LED) targets mounted on a black horizontal stimulus arc. One LED was mounted in the centre, and one at 17.6 cm either side of centre and another at 35.4 cm either side of centre. The stimulus arc was placed at measured distances in order to elicit saccades of 5, 7.5, 10, 15 and 20° eccentricity both to the left and to the right. The nearest target distance was 100 cm and so the slightly different vergence angles were assumed to have a negligible effect. This range of target eccentricities was chosen since it enabled the main sequence to be determined and was within the measurement range of the eye tracker. The order of target eccentricity was randomised and a total of 40 target illuminations (20 to the left and 20 to the right) were presented at each eccentricity, in a pseudo-random order. As the peripheral target was illuminated the central target was extinguished. Subjects were instructed to keep their eyes on the illuminated target all the time and to follow it with their eyes only when it moved. Only centrifugal saccades were used for analysis.

Figure 3.2. Horizontal OKN quick phase amplitudes



Plots to illustrate the range of quick phase amplitudes elicited at different stimulus speeds. As stimulus velocity increased the probability of getting large amplitude quick phases increased.

3.2.3 Data analysis

Eye movements recorded using IR and EOG were sampled and filtered as explained in Chapter 2. The analysis program described in Chapter 2 was used to determine the amplitude, duration and peak velocity of all the saccades and OKN quick phases and also the velocity of the OKN slow phases.

The main sequence for duration can be quantified by calculating the slope and intercept of a linear regression fitted over a restricted range. Traditionally investigators have taken 5^{o} as the amplitude threshold for linear regression calculations. However, we consider that linearity begins lower than this. Thus, we used a threshold of 4^{o} for the linear regression calculations in order that a greater number of saccades/OKN quick phases would be included in these calculations. Linearity is also lost at the larger amplitude end of the spectrum but as such large eye movements were beyond the measurement range of the infrared eye tracker they were not recorded in this experiment.

We quantifiably compared saccade and quick phase dynamics. For each subject, regressions were fitted to the duration and peak velocity main sequences for saccades and for OKN quick phases (Figure 3.3) and the slope and intercept values were used for statistical purposes. The relation between peak velocity and amplitude is not a linear one (Figure 3.3b) and, therefore, before performing linear regressions a logarithmic (base 10) plot (Figure 3.3c) was constructed for each subject.

The slope and intercept values of the linear regression are co-dependent. Therefore, it was necessary to use a multivariate analysis of variance (MANOVA) in order to determine if there were statistical differences between saccades and OKN quick phases. The slope and intercept values of each subject were taken as the

dependent variables. Statistical significance was assumed at a p=0.05 level throughout.

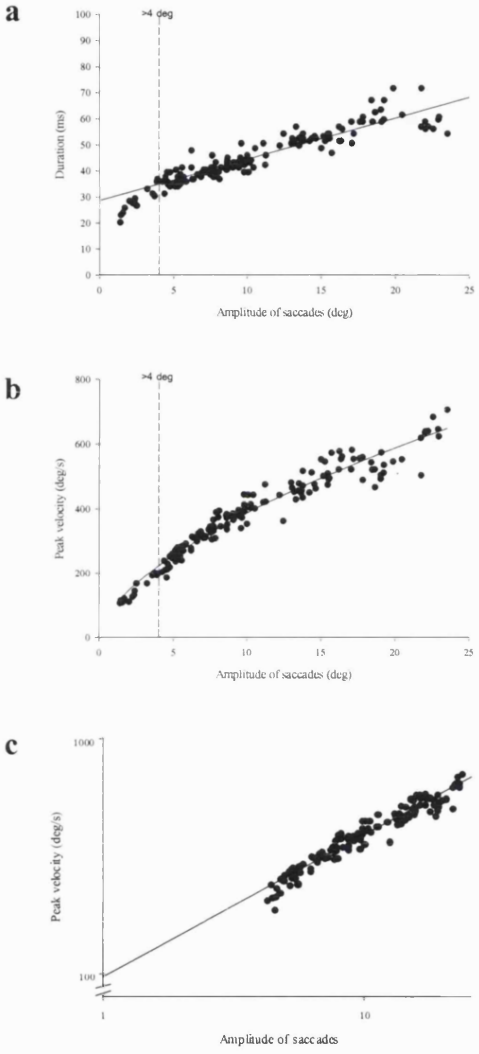


Figure 3.3. Typical saccadic main sequences for duration and peak velocity

These plots were derived from saccades recorded from subject SG using infrared limbal reflection. (a) Scatter plot for saccadic duration versus saccadic amplitude. Linear regression line for saccadic amplitudes >4° also shown. (b) Plot demonstrating the non-linear relation between saccadic peak velocity (PV) and saccadic amplitude (A). Curve fitted according to $PV = I.S^{logA}$, where I and S are the values of the linear regression intercept and slope for log PV versus log A. (c) Logarithmic plot of PV versus A, for saccadic amplitudes >4°. Linear regression line also shown.

3.3 Results

3.3.1 Horizontal OKN slow phase gain

Slow phase velocity gain decreased as the velocity of the optokinetic stimulus increased. The slow phase gain, at each stimulus speed is shown in Figure 3.4.

Idiosyncratic preferences for one direction of horizontal motion occurred. For three subjects (JH, CH, RH) the rightward OKN gain generally exceeded the OKN gain for leftward stimulus motion but for two further subjects (PV, MH) the reverse was true. In the other subjects (LP, LS, SG, RA, LH) a general gain difference was absent. The stimulus speed and slow phase gain are co-dependent; as stimulus speed increases slow phase gain decreases. Therefore, to determine if there were differences in the OKN slow phase gains for rightward motion compared to leftward motion it was necessary to perform a multivariate analysis of variance (MANOVA). This demonstrated that the OKN gains for rightward motion were not statistically different to those for leftward motion (p=0.93, Hotellings T-test).

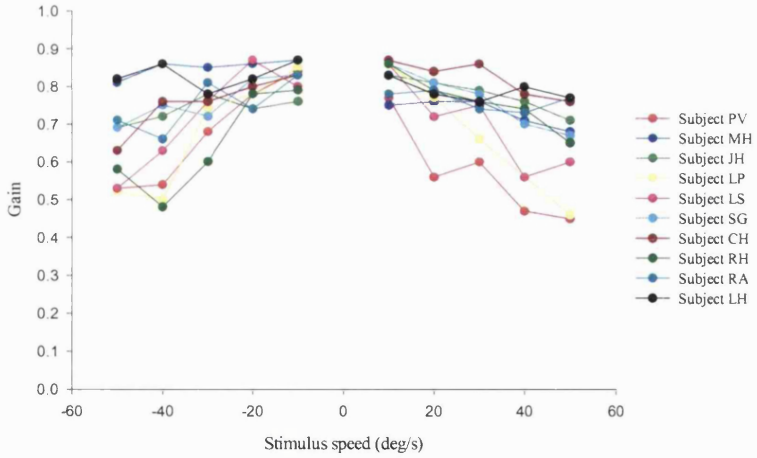


Figure 3.4. Horizontal OKN slow phase gain

Average horizontal OKN slow phase gain plotted against stimulus speed for 10 subjects. Negative values represent eye movements to the left. Data recorded using the infrared eye tracker.

Table 3.2. Horizontal OKN slow phase velocity gain

	Rightward moving stimulus (°/s)					Leftward moving stimulus (°/s)				
	10	20	30	40	50	10	20	30	40	50
PV	0.77	0.56	0.60	0.47	0.45	0.84	0.78	0.68	0.54	0.53
MH	0.75	0.76	0.76	0.71	0.68	0.87	0.86	0.85	0.86	0.81
JH	0.83	0.81	0.79	0.76	0.71	0.76	0.74	0.78	0.72	0.69
LP	0.86	0.77	0.66	0.56	0.46	0.85	0.78	0.74	0.50	0.52
LS	0.86	0.72	0.75	0.56	0.60	0.80	0.87	0.76	0.63	0.53
SG	0.86	0.81	0.78	0.70	0.67	0.83	0.82	0.72	0.75	0.69
CH	0.87	0.84	0.86	0.78	0.76	0.83	0.80	0.76	0.76	0.63
RH	0.86	0.79	0.76	0.74	0.65	0.79	0.78	0.60	0.48	0.58
RA	0.78	0.79	0.74	0.73	0.77	0.83	0.74	0.81	0.66	0.71
LH	0.83	0.78	0.76	0.80	0.77	0.83	0.78	0.76	0.80	0.77
Mean	**0.83**	**0.76**	**0.75**	**0.68**	**0.65**	**0.82**	**0.80**	**0.75**	**0.67**	**0.65**
±	±	±	±	±	±	±	±	±	±	±
SE	**0.01**	**0.02**	**0.02**	**0.04**	**0.04**	**0.01**	**0.01**	**0.02**	**0.04**	**0.03**

Horizontal OKN slow phase velocity gain for each of the ten subjects at every stimulus speed and in each direction. Mean and standard error (SE) for all the subjects also shown

3.3.2 Comparison of horizontal saccades with horizontal OKN quick phases recorded using the infrared limbus eye tracker

For a given amplitude, OKN quick phases tended to have a longer duration than saccades (Figure 3.5). However, statistical testing demonstrated that these differences were *not* significant (Hotellings T-test, p=0.73, for FEMs to the right; p=0.53 for FEMs to the left, see Table 3.3).

There were also differences in the peak velocities of saccades and OKN quick phases. For a given amplitude, OKN quick phases tended to have a lower peak velocity compared to saccades (Figure 3.6). Statistical testing demonstrated that these differences *were* significant (p=0.01 for FEMs to the right; p=0.04 for FEMs to the left).

Figure 3.5. Saccadic and OKN quick phase main sequences for duration

Scatter plots of the saccadic and OKN quick phase main sequences for duration for each subject. Data recorded using the infrared eye tracker. Continued overleaf.

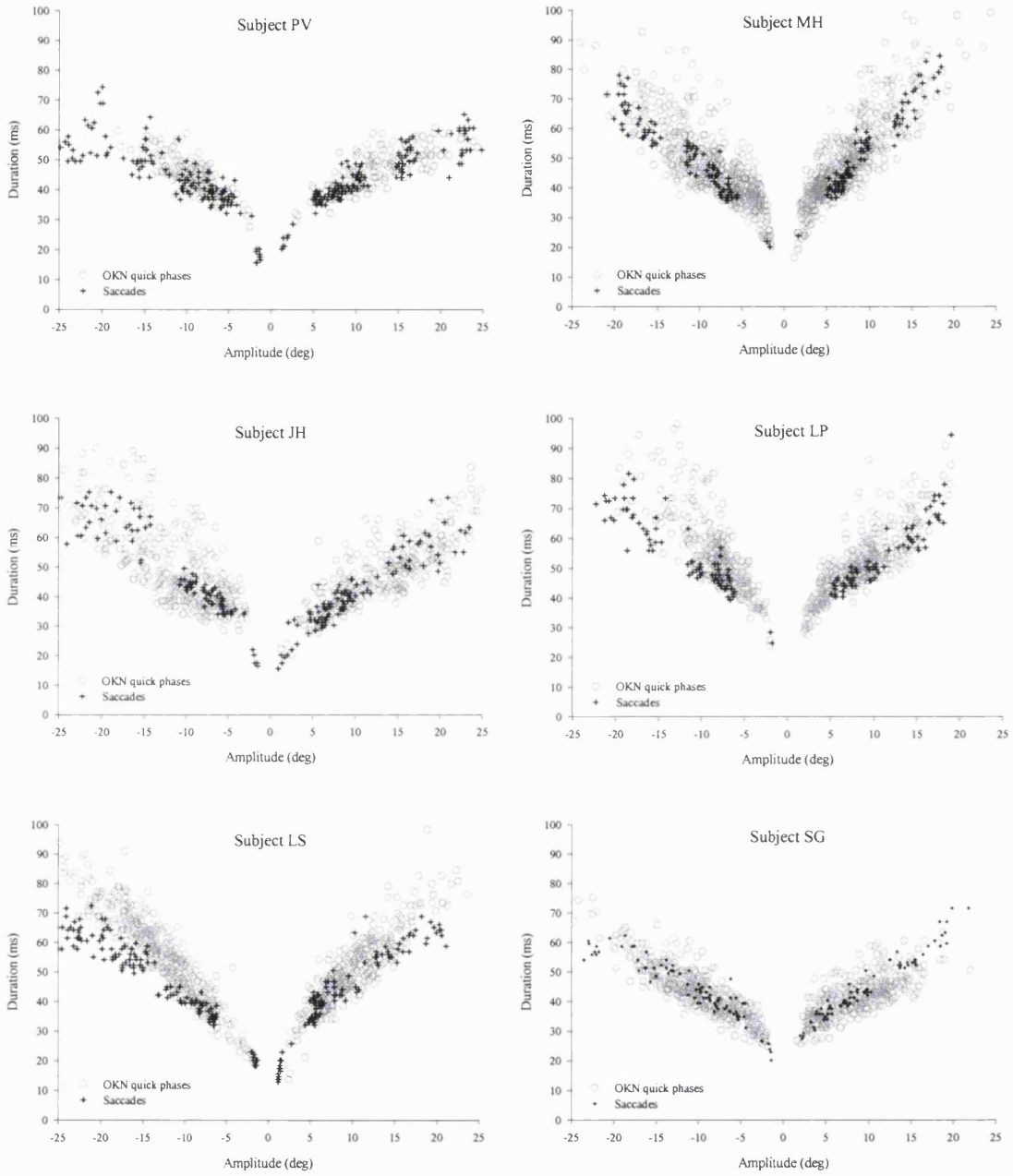


Figure 3.5. Continued-Saccadic and OKN quick phase main sequences for duration

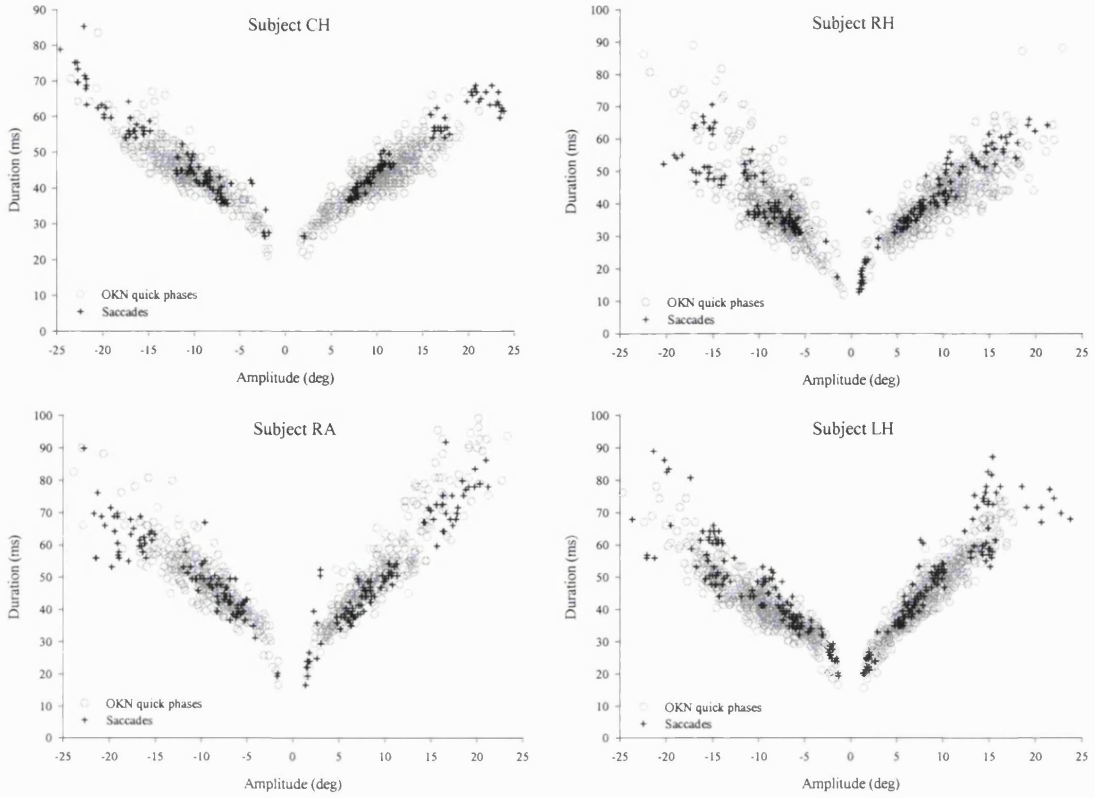


Figure 3.6. Saccadic and OKN quick phase main sequences for peak velocity

Scatter plots of the saccadic and OKN quick phase main sequences for peak velocity for each subject. Data recorded using infrared limbal reflection. Continued overleaf.

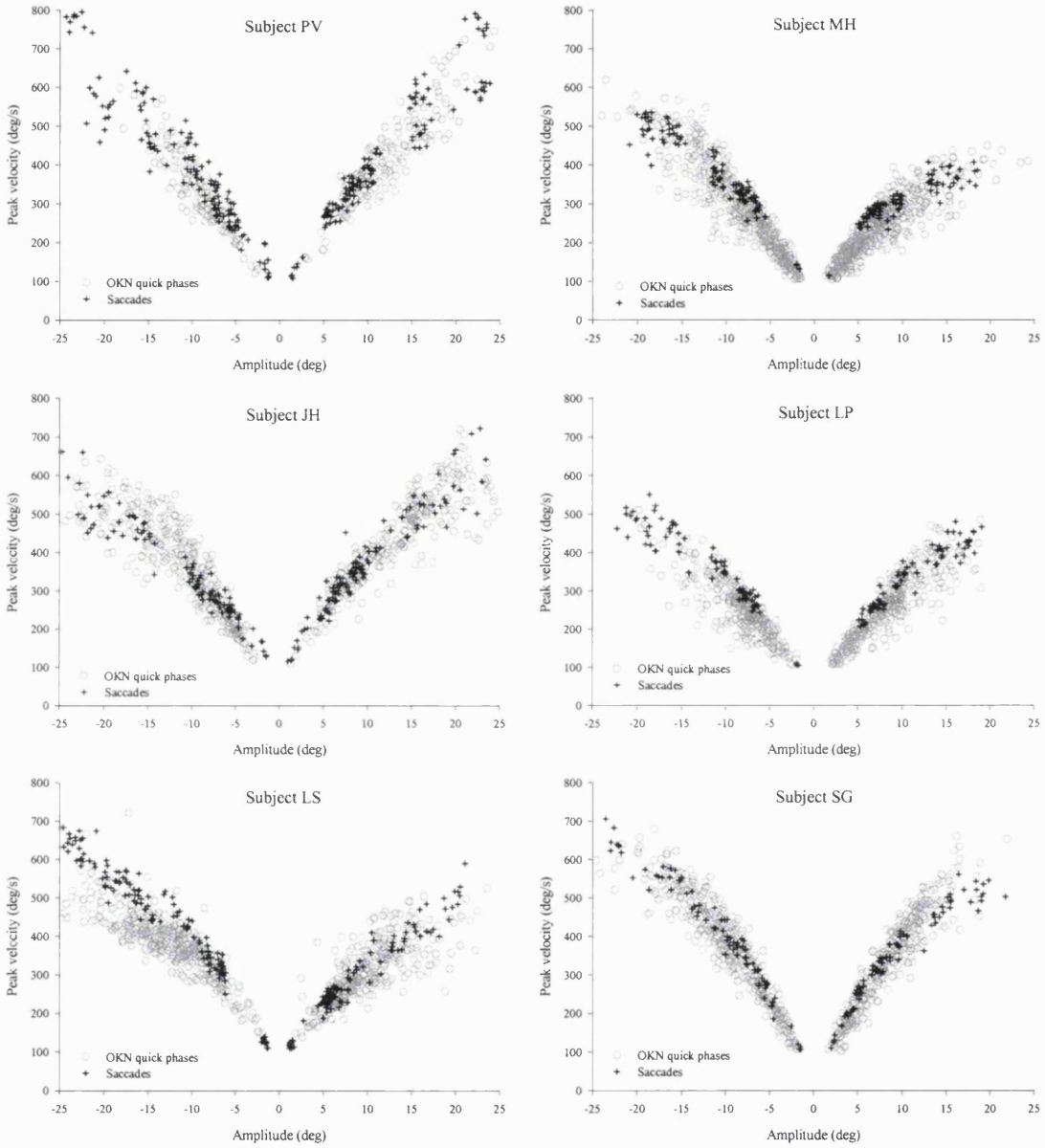


Figure 3.6. Continued-Saccadic and OKN quick phase main sequences for peak velocity

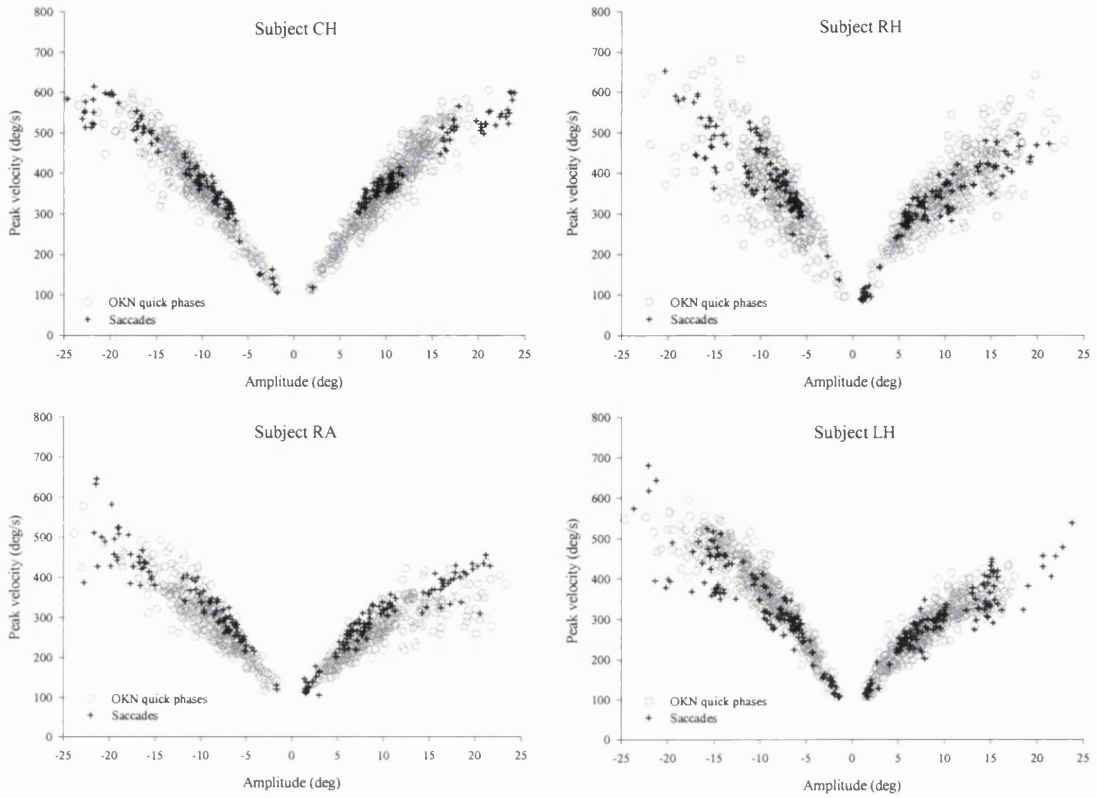


Table 3.3. Main sequence parameters recorded using infrared limbal reflection

	MAIN SEQUENCE FOR DURATION								MAIN SEQUENCE FOR PEAK VELOCITY							
	SACCADES				OKN QUICK PHASES				SACCADES				OKN QUICK PHASES			
	RIGHT		LEFT		RIGHT		LEFT		RIGHT		LEFT		RIGHT		LEFT	
	S	I	S	I	S	I	S	I	S	I	S	I	S	I	S	I
Subject	msec/°	msec	msec/°	msec	msec/°	msec	msec/°	msec								
PV	1.54	30.79	1.55	31.35	1.68	30.82	1.97	30.82	0.66	1.94	0.65	1.94	0.66	1.86	0.75	1.76
MH	3.10	22.33	2.18	25.79	2.87	28.31	2.34	27.65	0.34	2.16	0.51	2.05	0.54	1.91	0.67	1.86
JH	1.81	23.43	2.04	26.04	1.62	26.47	1.89	28.21	0.60	1.99	0.57	1.97	0.62	1.95	0.69	1.85
LP	2.31	28.76	2.02	30.41	2.36	30.81	3.02	29.36	0.57	1.94	0.54	1.99	0.70	1.78	0.73	1.77
LS	1.97	27.25	1.77	24.06	2.54	24.10	2.73	20.79	0.56	1.95	0.54	2.06	0.56	1.94	0.46	2.08
SG	1.94	25.95	1.51	28.52	1.62	29.90	1.65	27.09	0.59	1.99	0.63	1.97	0.79	1.78	0.69	1.90
CH	1.73	27.18	2.04	24.30	1.64	26.21	1.49	28.86	0.48	2.10	0.54	2.04	0.70	1.86	0.73	1.83
RH	2.22	21.97	2.13	20.82	1.88	23.47	2.21	20.97	0.40	2.15	0.46	2.15	0.48	2.06	0.52	2.08
RA	3.03	20.15	1.94	29.67	3.18	21.72	2.23	27.75	0.45	2.04	0.53	2.01	0.51	1.94	0.62	1.89
LH	2.62	25.34	2.43	22.56	2.71	22.19	1.96	22.61	0.43	2.07	0.57	1.99	0.47	2.01	0.59	1.99
Mean	**2.23**	**25.32**	**1.96**	**26.35**	**2.21**	**26.40**	**2.15**	**26.41**	**0.51**	**2.03**	**0.55**	**2.02**	**0.60**	**1.91**	**0.65**	**1.90**
±	±	±	±	±	±	±	±	±	±	±	±	±	±	±	±	±
SE	**0.17**	**1.05**	**0.09**	**1.12**	**0.19**	**1.10**	**0.15**	**1.14**	**0.03**	**0.03**	**0.02**	**0.02**	**0.03**	**0.03**	**0.03**	**0.04**

The slope (S) and intercept (I) for the duration-amplitude relation were obtained from a linear regression of the main sequence for duration for amplitudes >4°. The slope (S) and intercept (I) values for the peak velocity-amplitude relation were obtained from a linear regression of the logged main sequence for peak velocity for amplitudes >4° (see Methodology and Figure 3.3b, c). Mean and standard errors (SE) for all subjects also shown.

3.3.2 Comparison of results obtained using electro-oculography with those obtained from the infrared eye tracker

As with the data recorded by IR, the differences in the main sequence for duration of saccades and quick phases recorded by EOG were not significantly different (Hotellings T-test, p=0.14, for FEMs to the right; p=0.06 for FEMs to the left, see Table 3.4). Similarly, as with the peak velocities recorded using IR, the differences between the main sequence for peak velocity of saccades and quick phases recorded by EOG *were* significantly different (p=0.01 for FEMs to the right; p=0.01 for FEMs to the left, see Table 3.4).

The main sequence parameters for duration and peak velocity recorded using EOG were compared with those recorded using IR. The slope and intercept values for each of the ten subjects were taken as the dependent variables and the recording devices were taken as the independent factors. The results for saccades were analysed separately to those for OKN and eye movements to the right separately from those to the left. No statistical differences were found. For saccades the differences in the duration values recorded by IR and EOG were not statistically significant (p=0.09 for saccades to the right; p=0.44 for saccades to the left) nor were the peak velocity values (p=0.93 for saccades to the right; p=0.32 for saccades to the left). Also, for OKN quick phases the differences in the duration values recorded by IR and EOG were not statistically significant (p=0.33 for OKN quick phases to the right; p=0.08 for quick phases to the left) nor were the peak velocity values (p=0.41 for quick phases to the right; p=0.34 for quick phases to the left).

Table 3.4. Main sequence parameters recorded using electro-oculography

	MAIN SEQUENCE FOR DURATION								MAIN SEQUENCE FOR PEAK VELOCITY							
	SACCADES				OKN QUICK PHASES				SACCADES				OKN QUICK PHASES			
	RIGHT		LEFT		RIGHT		LEFT		RIGHT		LEFT		RIGHT		LEFT	
	S	I	S	I	S	I	S	I	S	I	S	I	S	I	S	I
Subject	msec/°	msec	msec/°	msec	msec/°	msec	msec/°	msec								
PV	1.50	28.00	1.71	27.19	1.68	30.72	1.78	29.42	0.65	1.95	0.63	1.98	0.65	1.81	0.75	1.80
MH	2.57	19.43	2.46	23.08	3.22	19.63	3.43	19.95	0.31	2.14	0.48	2.06	0.50	1.90	0.61	1.88
JH	2.27	16.44	2.33	16.24	2.97	17.83	2.83	18.34	0.59	2.02	0.57	1.99	0.63	1.96	0.65	1.90
LP	2.18	27.12	2.39	27.80	2.69	28.35	3.25	26.07	0.56	1.93	0.56	1.96	0.65	1.81	0.69	1.75
LS	1.71	27.19	1.63	26.85	2.39	26.32	2.48	28.87	0.63	1.90	0.50	2.01	0.57	1.87	0.50	2.01
SG	1.92	25.34	1.58	28.60	1.63	26.85	2.13	23.43	0.57	1.96	0.60	1.99	0.75	1.73	0.73	1.85
CH	1.96	26.97	2.05	26.47	1.97	25.80	2.42	27.20	0.49	2.11	0.51	2.07	0.66	1.90	0.70	1.84
RH	1.85	21.67	1.78	18.38	2.17	19.00	2.10	15.71	0.41	2.15	0.43	2.12	0.48	2.07	0.48	2.08
RA	2.86	18.50	2.35	26.01	3.34	21.15	3.26	18.61	0.40	2.07	0.49	2.03	0.45	1.96	0.51	1.90
LH	2.30	19.11	2.44	18.59	2.43	19.51	2.53	19.73	0.35	2.13	0.46	2.06	0.41	1.99	0.57	1.96
Mean	**2.11**	**22.98**	**2.07**	**23.92**	**2.45**	**23.52**	**2.62**	**22.73**	**0.50**	**2.04**	**0.52**	**2.03**	**0.58**	**1.90**	**0.62**	**1.90**
±	±	±	±	±	±	±	±	±	±	±	±	±	±	±	±	±
SE	**0.13**	**1.39**	**0.11**	**1.44**	**0.19**	**1.45**	**0.18**	**1.55**	**0.04**	**0.03**	**0.02**	**0.02**	**0.03**	**0.03**	**0.03**	**0.03**

The slope (S) and intercept (I) for the duration-amplitude relation were obtained from a linear regression of the main sequence for duration for amplitudes >4°. The slope (S) and intercept (I) values for the peak velocity-amplitude relation were obtained from a linear regression of the logged main sequence for peak velocity for amplitudes >4° (see Methodology and Figure 3.3b, c). Mean and standard errors (SE) for all subjects also shown.

3.4 Discussion

3.4.1 Horizontal OKN slow phase gain

It has previously been shown that slow phase velocity gain decreases as the velocity of the optokinetic stimulus increases (Dichgans *et al.*, 1973; Hood, 1975; van Die and Collewijn, 1982; van den Berg and Collewijn, 1988; Holm-Jensen and Peitersen, 1997). This trend was seen in our data (Figure 3.4). For the ten subjects in our study the greatest slow phase velocity gain recorded using IR (0.87) matches closely that reported in the literature. Van den Berg and Collewijn (1988) assessed the optokinetic response to a full-field stimulus rotating at velocities of 9 to 57°/s. They found that the slow phase velocity gain was always less than 0.85. For full-field optokinetic stimulation at speeds ranging from 6 to 60°/s van Die and Collewijn (1982) also reported gains of up to about 0.85.

Although there were idiosyncratic preferences for one direction of horizontal motion, when the ten subjects were taken as a group these preferences for rightward or leftward motion were not statistically significant. Van den Berg and Collewijn (1988) also reported that there was no overall preference for rightward or leftward stimulus motion, as did van Die and Collewijn (1982). However, both groups of investigators, like us, noted individual preferences for one direction.

Since the slow phase OKN gain recorded from our subjects concurs with ranges previously reported by others, we can be certain that we had representative OKN data with which to compare the temporal characteristics of saccades.

3.4.2 The main sequence for duration

The saccadic main sequence

Our saccadic data lies within previously reported ranges. For the *saccadic* main sequence for duration recorded by IR we found individual values for the slope that ranged from 1.51 to 3.10 ms/° (mean 2.10 ms/°) and an intercept that ranged between 20.15 and 31.35 ms (see Table 3.3). In the literature individual values for the slope range from 1.5 to 3 ms/° (with means between 2 and 2.7 ms/°). The intercept values in these studies typically range from 20 to 30 ms (Robinson, 1964; Yarbus, 1967; Körner, 1975; Baloh *et al.*, 1975a).

Collewijn *et al.* (1988a) differentiated between centrifugal and centripetal saccades and in four subjects found similar values for centripetal saccades to the ones we found for centrifugal saccades. They found that centrifugal saccades had a lower intercept and steeper slope. The differences between our results and theirs may be explained, at least in part, by the fact that we elicited reflexive saccades, whereas Collewijn *et al.* elicited voluntary saccades (at the pace of a metronome set at 52 beats/min). It is believed that the neural mechanisms generating reflexive and voluntary saccades are at least partially different and this could result in different metrics. Erkelens and Hulleman (1993) attempted to determine the neural mechanisms controlling reflexive and voluntary saccades by looking at the effects of lesions. They concluded that voluntary saccades are most probably generated via the frontal eye field pathways, whereas collicular pathways seem to be more important in the control of reflexive saccades.

Reflexive saccades versus OKN quick phases

Statistical analysis demonstrated that the saccadic main sequence for duration was not significantly different from the OKN quick phase main sequence for duration. In animals it has been demonstrated that the main sequence for duration for spontaneous saccades is the same as that for VN quick phases (Ron *et al.*, 1972; Guitton and Mandi, 1980). It has also been shown that both spontaneous saccades and the quick phases of VN are similarly affected by light and darkness. Three studies have compared the main sequences for duration of saccades and OKN quick phases in humans and concluded that they were similar (Mackensen and Schumacher, 1960; Jürgens and Becker, 1977; Jürgens *et al.*, 1981a). Mackensen and Schumacher (1960) tested only two subjects but concluded that the main sequence for duration of these FEMs were the same. They noted that the intrasubject differences were quite marked and that there were differences between FEMs made to the right compared to those made to the left. We also noted intrasubject differences and that for individual subjects there were directional differences. Jürgens and Becker (1977) and Jürgens *et al.* (1981a) compared optokinetic quick phases to voluntary saccades. They found that the main sequence for duration for these two FEMs scattered around the same regression line. Our results support their findings.

The final common pathway for all horizontal saccades involves burst neurons in the paramedian pontine reticular formation (PPRF). These neurons provide the immediate premotor command signal, the pulse, which is sent to the oculomotor nuclei. Results of studies in monkeys using lesions, extracellular recording and stimulation have suggested that identical premotor neural circuits generate saccades and the quick phases of nystagmus.

Lesion studies

Lesions of the PPRF have been shown to impair all fast eye movements equally (Bender and Shanzer, 1964; Cohen and Henn, 1972; Henn *et al.*, 1984). Saccades and the quick phases of nystagmus (OKN and VN induced by caloric stimulation or by rotation in darkness) to the ipsilateral side are initially abolished after PPRF lesions and later are of small amplitude and low velocity. In some monkeys rapid eye movements into the ipsilateral hemifield have been permanently abolished after PPRF lesions.

Extracellular recordings

Recordings of pontine electrical activity during eye movements demonstrated that potentials in the PPRF precede FEMs by 10-20 ms (Cohen and Feldman, 1968; van Gisbergen *et al.*, 1981; Strassman *et al.*, 1986; Hepp *et al.*, 1989). These potentials were similar during saccades and the quick phases of nystagmus (VN induced by caloric stimulation) and were not found during pursuit movements or the slow phases of nystagmus. Similarly, Keller (1974) found that the characteristics of burst cells in the PPRF were identical during saccades and vestibular quick phases (induced by rotation). No differences in the onset, duration or intraburst firing frequency during saccades and vestibular quick phases were found.

Cohen and Henn (1972) identified two major groups of neurons in the PPRF that changed frequency between 12 and 20 ms before a FEM. One of these groups was active during FEMs (burst units) and the second group was inhibited during FEMs (pause units). In none of these units was there any apparent difference in activity whether the FEM was a saccade, or a quick phase of optokinetic or vestibular nystagmus.

Stimulation studies

Cohen and Komatsuzaki (1972) induced ipsilateral eye movements in monkeys by electrical stimulation of the PPRF. Depending on the strength, frequency and duration of stimulation, either eye movements similar to the slow phases of nystagmus and pursuit movements or saccades and the quick phases of nystagmus could be induced.

Keller (1974) electrically stimulated the area in the pontine reticular formation that contains saccade pause units. When the stimulus was applied and maintained all voluntary saccades were eliminated, as were the quick phases of OKN and VN (rotational).

These studies lend considerable support to the concept that, in monkeys, much of the same lower brainstem neural pathways are shared by saccades and nystagmus quick phases. Our findings provide quantitative evidence that in humans, also, saccades share the same pre-motor circuitry as OKN quick phases. Furthermore, this suggests that measurement of the OKN quick phase main sequence for duration in infants or unco-operative patients could be used clinically to assess the functioning of the saccade system (see following chapter).

3.4.3 The main sequence for peak velocity

The saccadic main sequence

We will first consider the main sequence for peak velocity for *saccades* in order to establish that they lie within previously reported values. The main sequence relationship that we found between peak velocity and saccade amplitude is typical of

that which has been reported previously (Bahill *et al.*, 1975; Schmidt *et al.*, 1979; Jürgens *et al.*, 1981b).

Although the general shape of the peak velocity-amplitude relationship does not differ greatly among several investigators, the actual values of the peak velocities do. This is illustrated by the range of mean peak velocities given for 20° saccades (right and left saccades pooled): Boghen *et al.* (1974) reported a mean peak velocity of about 375°/s, a mean peak velocity of about 420°/s can be derived from the data of Baloh *et al.* (1975a) and Bahill *et al.* (1981) found a mean peak velocity of 657°/sec. For all our saccadic data taken together, the mean peak velocity of a 20° saccade recorded by IR was 540°/s with a 95% confidence interval between 400 and 679°/s. There does not appear to be any systematic variations that can be attributed to the different recording techniques employed. Nevertheless, bandwidth limitation in the recording of eye position and the derivation of eye velocity can lead to an underestimation of peak velocities (Bahill *et al.*, 1981). However, as variability between and within subjects can be considerable, even in the same laboratory, other factors must be important. Bahill *et al.* (1981) considered fatigue to be a source of variability and therefore eliminated from their data any saccades that were noticeably slower than optimum. Thus, the higher peak velocities reported by Bahill *et al.* may be explained by their focus on the "optimal edge". Another possibility for the different reported values for peak velocity is a systemic dependence of saccadic parameters upon the direction (nasal or temporal, centrifugal or centripetal) or the orientation of the saccade within the oculomotor range (symmetrical around the primary position, or within a peripheral sector of the range) (Collewijn *et al.*, 1988a). Thus, currently there are no accepted inter-laboratory standard values for what should be considered a normal peak velocity for a given saccadic amplitude. Therefore,

before using measurements of the main sequence for peak velocity, it will be necessary to establish our own normative values that best reflects our procedures.

Reflexive saccades compared to OKN quick phases

We found that OKN quick phases tended to have a lower peak velocity compared to reflexive saccades. The fact that we found differences between the peak velocities of these FEMs but no differences in the duration may imply that reflexive saccades and OKN quick phases have slightly different trajectories. In the literature OKN quick phases in humans have variously been reported to have a lower peak velocity than saccades (Henriksson *et al.*, 1980), to have a lower peak velocity only at greater amplitudes (>20°) (Dichgans *et al.*, 1973) or to be indistinguishable from saccades (Mackensen and Schumacher, 1960; Sharpe *et al.*, 1975; Jürgens and Becker, 1977; Jürgens *et al.*, 1981a). The differences may be partly explained by the type of saccades that were used for comparison. The velocity of saccades differs depending on how it is elicited (in the light or dark, reflexively or voluntarily). For example, saccades in the dark are about 10% slower than equally sized saccades between visible fixation points (Becker and Fuchs, 1969; Becker and Klein, 1973). The peak velocity of saccades also differs depending on the direction of the saccade. It is well documented that centripetal saccades are faster than centrifugal saccades (Frost and Pöppel, 1976; Abel *et al.*, 1979; Jürgens *et al.*, 1981b; Inchingolo *et al.*, 1987; Pelisson and Prablanc, 1988; Collewijn *et al.*, 1988a). In our experiment we compared centrifugal saccades with OKN quick phases. We chose to do this because quick phases are essentially centrifugal movements since quick phases move the eyes in the opposite direction to stimulus movement (see Chapter 5).

A further consideration is the fact that in humans the OKN response differs depending on the instructions given by the investigators (look- or stare-OKN, see Chapter 1). Becker (1989) suggested that the quick phases of look-OKN could resemble goal directed saccades, whereas the quick phases of stare-OKN, which do not profit from the selection of visual targets, may be slower. We attempted to elicit stare-OKN by instructing our subjects to look straight ahead, to keep the curtain as clear as possible and not to track any individual target. Therefore, Becker's argument may explain why we found that the peak velocities of saccades were higher than the quick phases of OKN. However, due to the restrictions of our recording equipment (the eye tracker had a linear range of ± 25°), we had to encourage our subjects to keep their eyes in the centre. This resulted in the subjects having to, at times, actively move their eyes to the centre. Therefore, the OKN that we elicited was most probably a mix of look- and stare-OKN.

Another consideration is the range of amplitudes that are compared. Henriksson *et al.* (1980) found that the differences between the peak velocities of saccades and quick phases of nystagmus were more pronounced at greater amplitudes. Dichgans *et al.* (1973) found that the differences between the peak velocities of saccades and OKN quick phases were statistically significant only at amplitudes greater than 20° (and only to the left). This may explain why investigators who compared only a limited range of amplitudes (0-20° Mackensen and Schumacher, 1960; 0-10° Sharpe *et al.*, 1975) found no differences in the peak velocities of saccades and OKN quick phases. We limited our comparisons to amplitudes below 25°, because of the restrictions in the linear range of the eye tracker.

The peak velocity differences that we found are slight enough that it seems unnecessary to hypothesise separate neural circuits for the generation of these two

types of FEM. The small differences may only indicate that FEMs are initiated in the same neural circuits but in slightly different ways. Henriksson *et al.* (1980) suggested that the normal contraction of the antagonistic muscle present only during the quick phase of nystagmus (Shimazu, 1972) might explain a difference in velocity between quick phases and saccades. Another factor is that compared to the quick phases of OKN higher visual attention is required to elicit saccades. During saccades the subject is alert and actively performing the task, while during OKN, quick phases are released automatically. Henriksson *et al.* (1980) suggested that the higher velocity of saccades might in part be explained by a more powerful excitation of pontine neurons caused by volition or related to alertness caused by volition.

3.4.4 Infrared eye tracker compared to electro-oculography

The duration values we obtained using EOG agreed well with those recorded using IR. Scatter, however, was greater owing to the increased noise inherent in the EOG measurement technique. Bahill *et al.* (1981) established their normative database of saccadic durations using IR. When compared with other laboratories where EOG had been used, Bahill and co-workers' data coincided reasonably well (see Becker, 1989). On the other hand, Baloh *et al.* (1975b) using EOG, reported much larger values for saccadic durations. However, this is probably the result of recording with a low cut-off frequency and processing the data with a digital filter averaging samples at 15 ms apart in time (67 Hz).

Saccadic durations recorded using EOG have also been compared to those recorded using a magnetic search coil. Becker (1989) used EOG to measure the main sequence for duration in twenty-six subjects and compared the results to values recorded using a magnetic search coil in ten subjects. With similar signal processing

and analysis procedures these EOG and magnetic search coil measurements led to virtually identical results.

We also found that the peak velocity main sequence characteristics for saccades and OKN quick phases were similar whether recorded using IR or EOG. In the literature saccadic peak velocities recorded using IR (Boghen *et al.*, 1974; Schmidt *et al.*, 1979) are comparable with those recorded using EOG (Baloh *et al.*, 1975b; Becker, 1989). Clearly different from most other work, with its extremely large peak velocities, is the normative database of Bahill *et al.* (1981). However, these differences are unlikely to be due to the use of IR, but rather caused by their focus on the 'optimum edge' (see above).

Our results, together with those discussed above, confirm that in the clinical setting it would be suitable to use EOG to measure the duration and peak velocity of saccades and OKN quick phases.

3.5 Conclusion

Previously there was no consensus as to whether the temporal characteristics of horizontal saccades and horizontal OKN quick phases are the same. Therefore we compared, in ten normal adult subjects, horizontal centrifugal saccades with horizontal OKN quick phases. We found, using both infrared limbal reflection and electro-oculography, that the main sequence for duration of horizontal saccades is not significantly different from that of horizontal OKN quick phases. The main sequence for peak velocity of horizontal saccades is different from that of horizontal OKN quick phases; OKN quick phases have a lower peak velocity. However, these differences are slight enough that they are unlikely to be of clinical significance. We

suggest that recording OKN quick phases by electro-oculography may be a simple means for approximating the saccadic main sequence.

The slight differences in the peak velocities of horizontal saccades and horizontal OKN quick phases may be explained, at least in part, by the fact that they represent different tasks for the visual system.

Chapter 4 - Clinical Application of the Horizontal OKN Quick Phase Main Sequence

4.1 Introduction

If saccades fall outside the normal main sequences for duration and peak velocity they are defined as being too fast or too slow. In order to identify patients with slow saccades it is preferable to record their main sequences for duration and peak velocity by eliciting a large number of saccades over a range of amplitudes (Baloh *et al.*, 1975a). This can be difficult to achieve in infants and unco-operative patients, or in those who already have difficulty in initiating saccades. Indeed, in children with intermittent saccade initiation failure ("ocular motor apraxia"), it is crucial to detect any slowing of saccades, as this can distinguish progressive neurological disease from the more benign classic congenital saccade initiation failure (Cogan's apraxia) (Harris *et al.*, 1999).

In the previous chapter we showed that the temporal characteristics of horizontal saccades and OKN quick phases are similar. In this chapter we shall describe how we investigated the possibility of measuring the speed of OKN quick phases as a substitute for measuring saccade speed in infants and children. Two issues were considered:

(1) Since little is known about saccades in infants and children we approximated the main sequence by measuring OKN quick phases from a group of infants. We looked at the main sequence for duration and for peak velocity and compared these with those recorded from adult subjects.

(2) To determine if examination of OKN quick phases has a clinical role in identifying infants and children with abnormal saccades we examined children with Gaucher disease, a disease that is known to be associated with slow saccades. This is rare condition but all children with Gaucher disease in the UK are assessed at Great Ormond Street Hospital as this is the supraregional centre for the disease.

4.2 Experiment 1: The OKN main sequence in infants

4.2.1 Introduction

The assessment of eye movements in infants is difficult and can be unreliable in the clinical situation. The oculomotor system in the healthy neonate is immature, and therefore the eye movements seen in neonates should be distinguished from pathologically abnormal eye movements. Knowledge of normal eye movement development allows a more precise clinical assessment of oculomotor pathology in infants and children.

Studies of saccades, of horizontal OKN and of smooth pursuit support the general view that human infants have immature oculomotor systems (Dayton *et al.*, 1964; Aslin and Salapatek, 1975; Kremenitzer *et al.*, 1979; Salapatek *et al.*, 1980; Atkinson and Braddick, 1981; Aslin, 1981; Naegele and Held, 1982; Roucoux *et al.*, 1983; Hainline *et al.*, 1984 a & b; Roy *et al.*, 1989; Shea and Aslin, 1990; Harris *et al.*, 1993a; Harris *et al.*, 1994; Jacobs *et al.*, 1997; Lengyel *at al.*, 1998). These studies have also shown that the infant oculomotor system develops rapidly during the first three months of life and more slowly thereafter.

The main purpose of our experiment was to measure the quick phases of horizontal OKN in infants and compare them to those measured in adults. As a background to this experiment it is appropriate to review the current literature on saccades and horizontal OKN in normal infants.

4.2.1.1 Saccades in normal infants

Normal adults localise a target with a "normometric" primary saccade that brings the eyes on, or within 10% of the total target amplitude (Weber and Daroff, 1971; Becker, 1972; Barnes and Gresty, 1973). Any residual position error is corrected by a small secondary, and occasionally a tertiary saccade. Thus a small degree of hypometria is common in normal adults, however, hypermetria is much less frequent (Weber and Daroff, 1971). Healthy infants younger than 7 months, generate a highly variable primary saccade, which is frequently grossly hypometric and followed by a sequence of up to five more saccades before the target is reached (Aslin and Salapatek, 1975; Salapatek *et al.*, 1980; Regal *et al.*, 1983; Harris *et al.*, 1993a). These multiple hypometric saccades do not occur in normal older children, but are seen in pathological conditions such as cerebellar disease, saccade initiation failure and basal ganglia disorders (Leigh and Zee, 1999).

The underlying cause of these infantile saccades is not known. It is not the result of a fixed limitation on the amplitude of infant saccades since sometimes targets can be reached in a single saccade. Furthermore, larger target eccentricities invoke larger amplitude saccades. Aslin and Salapatek (1975), Regal *et al.* (1983) and Harris *et al.* (1993a) all reported that the proportion of sequences with two or more saccades increases with target eccentricity. It was also found that there was a decrease in the

proportion of multiple saccades with maturity, although adult levels were not reached by 7 months.

In contrast to these findings, Hainline and co-workers (Hainline et al., 1984b; Hainline and Abramov, 1995) found no evidence of hypometric saccades if infants simply scan visual patterns freely. In their study not only the accuracy of infant saccades but also their velocity was examined. If the pattern consisted of textures (i.e. line gradients and different sized checkerboards) they found that the infants, who were between 1 and 6 months old, and adults have similar saccadic main sequences for peak velocity. On the other hand, when the infants viewed patterns of different geometrical forms the main sequence for peak velocity had a lower slope. However, these findings need to be confirmed by further experiments because the eye movement measurements were not individually calibrated, the infant data was often composed of as few as 10 saccades per subject and, furthermore, the data contained a number of oblique saccades.

4.2.1.2 Horizontal OKN in normal infants

Large, patterned, horizontally moving, visual stimuli readily elicit a symmetric bi-ocular horizontal OKN from alert infants (Dayton and Jones, 1964; Kremenitzer *et al.*, 1979; Schor *et al.*, 1983). Both the slow and the quick phases of horizontal OKN can be elicited on the first day of life. However, as discussed in the Chapter 1, in the first few months of life humans have asymmetrical monocular horizontal OKN (mHOKN). Stronger OKN responses occur for a stimulus moving in the temporal-to-nasal (T-N) direction compared to the nasal-to-temporal direction (N-T). This nasal-temporal asymmetry declines during the first months of infancy until mHOKN becomes virtually symmetrical as in normal adults.

In the primate there is evidence for two components of OKN: an early component (OKNe) and a delayed component (OKNd) (see Chapter 1). In infants the presence of some smooth pursuit by 2-3 months (Dayton *et al.*, 1964; Aslin, 1981; Shea and Aslin, 1990) or earlier (Kremenitzer *et al.*, 1979; Roucoux *et al.*, 1983; Jacobs *et al.*, 1997; Lengyel *et al.*, 1998) suggests that OKNe is present from an early age. Also, Hainline *et al.* (1984a) found no evidence of slow build-up of small-field OKN in infants from 1 month of age and Kremenitzer *et al.* (1979) reported an example of quite rapid build-up in the newborn.

Only one previous study considered the temporal characteristics of OKN quick phases in infants (Hainline *et al.*, 1984a). It was reported that the slope of the main sequence for peak velocity in infants was lower than that of adults, which suggests that infants have slower OKN quick phases.

4.2.2 Methodology

4.2.2.1 Subjects

Subjects were healthy children of university and hospital staff and siblings of patients attending the hospital. The infants recruited were aged 2-18 months, full term (within a gestational period of 38-41 weeks) and healthy. Details of the test were explained verbally and in writing to the parents, and an informed consent form was signed. Twenty infants were recruited and useful recordings were obtained from eighteen.

All of the infants underwent a full ophthalmic examination. This included: -

(1) measurement of visual acuity or in the case of the youngest infants the ability to fix and follow a small target,

(2) assessment of binocularity (Lang stereotest), ocular motility and pupil reactions,

(3) examination of the anterior segment and fundus,

(4) a non-cycloplegic refraction.

No abnormalities were discovered in any of the infants.

Eight naïve adult subjects, with an age range of 21-32, acted as controls. None had any known neurological or ophthalmological disorder.

4.2.2.2 Eye movement recording

Horizontal eye movements were recorded using bi-temporal DC-coupled EOG. The subjects were also monitored at all times by a video camera. The video image and EOG signals were relayed to the adjacent room for recording. The EOG signal was superimposed upon the video image allowing the eye movement trace and the visual appearance of the eyes to be examined together (Jacobs *et al.*, 1992; Harris *et al.*, 1992). The comments of the two operators and the vocalisations of the subject were also recorded simultaneously with the eye movement signal.

Infants sat upright on a parent's lap facing the stimulus. The parent was asked to gently restrain the head during testing so as to minimise head movement. The recording sessions were performed while the infant was alert. If the infant was seen to become sleepy during the recording session noises were made to arose it. Saccades (for calibration) were tested first followed by horizontal OKN.

Adult controls underwent exactly the same testing procedures as the infants. They rested their heads against a headrest and were given no instructions except to keep the head still. Thus, as near a control to infant conditions as possible was provided.

4.2.2.3 Calibration

EOG has the disadvantage that the recordings must be calibrated in order to obtain quantitative information. In the most common calibration technique used with infants a small light spot is presented and rapidly moved from one position to another in the visual field (Aslin and Salapatek, 1975; Ornitz *et al.*, 1979; Salapatek *et al.*, 1980; Aslin, 1981). If the infant makes rapid eye movements in the appropriate direction shortly (i.e. within 1 second) after the target jumps it is assumed that the infant is following and ultimately fixating on the target. If the size of the eye movement varies by no more than 10% it is considered that a reasonable calibration has been obtained.

Metz (1984) used a prism to calibrate infant eye movement recordings. A prism was placed before the fixating eye. This produced an image jump and a resultant eye movement. By knowing the strength of the prism and the distance of the fixation target the eye movement could be used for calibration. This method has not found wide use in infant research. Possibly this is because it relies, like other methods, on an observer's judgement of the infant's initial fixation position and further assumes that the infant refixates the same point on the fixation target after application of the prism. Also, it is difficult to place a prism in front of an infant without them being distracted.

Finocchio *et al.* (1987) developed a technique in which the experimenter estimates the infant's fixation position by corneal reflection. A bright 1.7° light is slowly moved on a track in front of the child. The light is stopped at known horizontal angles and an observer, who moves with the target, sights along it to estimate and record when the corneal reflection is in the same position with respect to the pupil as it was when the infant fixated centrally. Finocchio *et al.* (1987) reported that for 2-

and 3-month old infants the amplitude of the eye movements recorded using this technique varies within ± 1.5° for targets placed at ±15°.

We felt that the best calibration technique to use with infants is one that is easy to perform. Thus we chose to calculate the change in EOG voltage during eye movements between 2 targets (including secondary and tertiary etc saccades). Two toy dogs were used as targets, each being 12 cm high and 6 cm wide, with a red LED light at the centre of the top of the head (Figure 4.1).

The toy dogs were positioned on a stand so that the LED lights were 18.5 cm either side of the primary position. The stand was placed at varying distances (between 106 cm and 35 cm from the infant) so that the LED lights were between 10 and 30° apart (across the midline). The right and left LED lights were alternatively illuminated and the toy dogs made noises to attract the infant's attention. An operator switched the LED lights on and off manually, illuminating one LED light as the infant was attending the other. The operator also announced the target positions and commented on the infant's behaviour, making special note of when saccades were appropriate to the target. The goal of the calibration procedure was to elicit as many saccades as possible and the stand was moved to different positions until the infant became restless or inattentive. Five to ten saccades were elicited at each stand position.

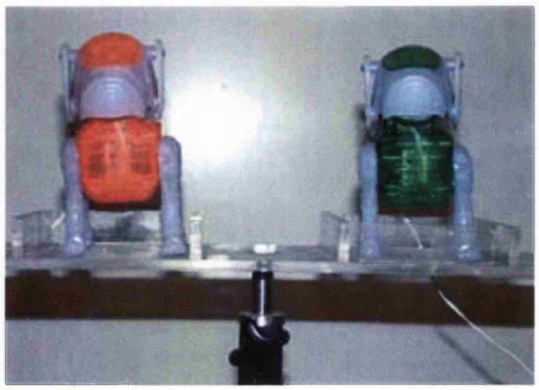


Figure 4.1. Calibration targets

The toy dogs used as targets during the calibration procedure.

4.2.3.4 Horizontal optokinetic nystagmus

The full-field, brightly coloured, optokinetic curtain described in Chapter 2 was the stimulus. Infants viewed the curtain with both eyes open. The curtain was rotated at 3 angular speeds; 25, 50 and 75°/s. However, the angular speeds relative to the infants were, on average, 30, 60, and 90°/s because the infant sitting on the parent's lap was closer to the curtain. The curtain rotated for 8 contiguous 24 second episodes at 30, 60, 90, 30, -30, -60, -90, -30°/s (adults at 25, 50, 75, 25, etc). The curtain was accelerated at $20°/s^2$ between episodes. A complete OKN session lasted 3 minutes and 30 seconds.

4.2.3.5 Data analysis

After the testing session the video recording of the calibration procedure was studied. Only movements between the targets in which the infant appeared to be

attentive and which were directionally appropriate were included in the calibration measurement. Eye movements associated with blinks or head movements were also discarded. For each infant, an average of 21 (±7) complete eye excursions were identified which could be used for the calibration measurement.

The calibration was calculated by the standard procedure used in our eye movement laboratory (see Chapter 2). The change in EOG voltage (mV) corresponding to each complete eye excursion between the two targets (including secondary, tertiary, etc saccades) was measured interactively by placing a cursor at the beginning and the end of the sequence of saccades. EOG-drift was negligible over the duration of each individual saccade. For each infant, the measured distance moved by the eyes in a saccadic sequence was plotted against the corresponding target separation (measured in degrees). In the majority of sessions there was a linear relationship, as seen in the typical example shown in Figure 4.2. A linear regression fitted to this plot allowed a conversion of the recorded signal from mV into degrees.

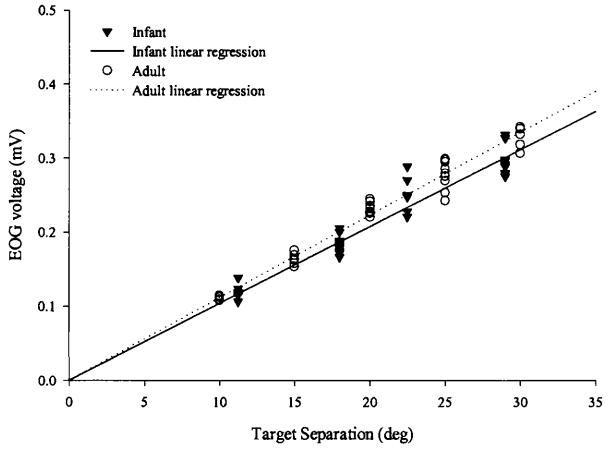


Figure 4.2. Calibration plot

Calibration of recording session from an adult and a 6-month old infant. Each symbol plots the change in EOG voltage for a saccade sequence versus the target separation for that sequence. The reciprocal of the slope of linear regression constrained to pass through the origin is used as the calibration factor for this session.

The video recording of the OKN session was also examined and periods of inattention and restlessness noted and excluded from further analysis. Our standard computer paradigm (see Chapter 2) was used to determine the slow phase velocity and the temporal characteristics of the OKN quick phases.

4.2.4 Results

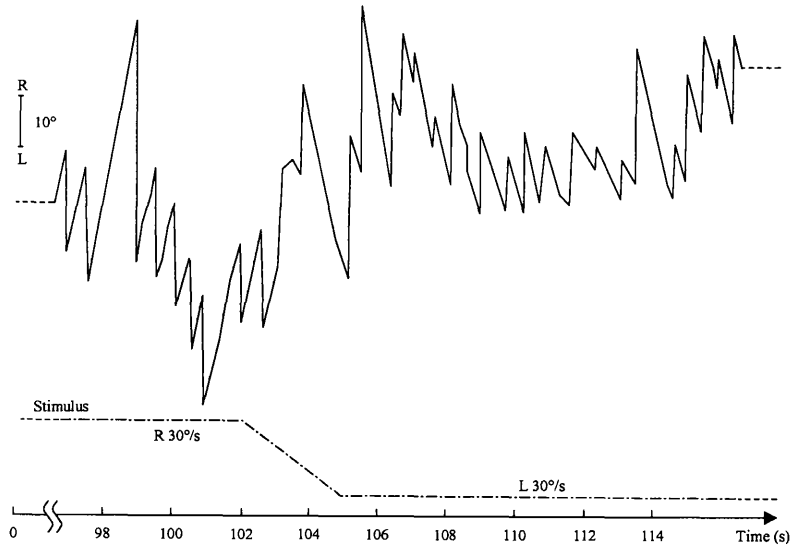
4.2.4.1 Saccades

All infants in the study frequently made multiple hypometric saccades during the calibration procedure. In this study we elicited 446 infant saccade sequences. Of these, 24.6% were singlets, 53.1% doublets, 16.8% triplets, 5.4% quadruplets, and 0.1% quintuplets. There were never more than 5 saccades in any sequence. In contrast, the adult controls tended to make a large primary saccade followed by one, or occasionally two, small corrective saccade. Very few infant sequences had a primary hypermetric saccade. Of the total 446 sequences, only 17 (3.8%) had secondary saccades that were in the opposite direction to the primary. This was similar to the adult controls (2.5%).

4.2.4.2 Horizontal OKN slow phase velocity

Examination of OKN slow phase velocity showed a prompt response to curtain speed. There was no slow build-up whether the curtain started from rest, accelerated to a higher speed, or reversed direction (Figure 4.3). Similarly there was no slow "build-down" when the curtain speed decreased or reversed.

Figure 4.3. Extract of horizontal OKN recorded from an infant



Extract of horizontal OKN during stimulus reversal recorded from a 15-month-old infant (FD) during curtain reversal from 30°/s rightward to 30°/s leftward. Note the prompt build-up of OKN after reversal. Stimulus acceleration was 20°/s^2.

We plotted slow phase velocity against time for each stimulus speed, in each direction (Figure 4.4). Linear regressions showed only very small changes in slow phase velocity within an episode. Thus, there is no evidence of any slow build-up or slow build-down of OKN during an episode.

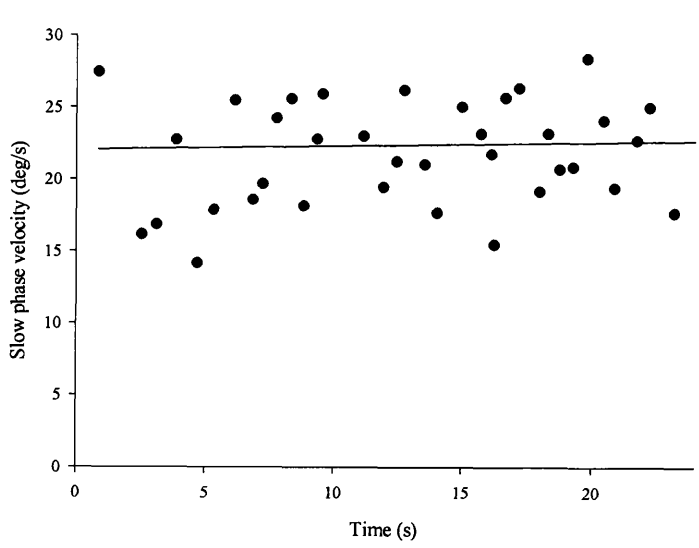


Figure 4.4. Slow phase velocity plotted against time

Representative plot of slow phase velocity against time for a 3-month-old infant (HW) during leftward curtain rotation at 30°/s. Linear regression line also plotted demonstrating that there is very little change in slow phase velocity with time and thus no evidence of slow build-up of OKN.

The average (mean) slow phase gain at each stimulus speed was calculated for each infant and adult. For a given stimulus speed, leftward and rightward episodes were combined to yield one measure of slow phase velocity. Infants had lower slow phase velocity gains compared to adults and there was a tendency for gain to increase with age (Table 4.1, Figure 4.5). Gain decreased with increasing stimulus speed in both infants and adults (Table 4.1, Figure 4.5).

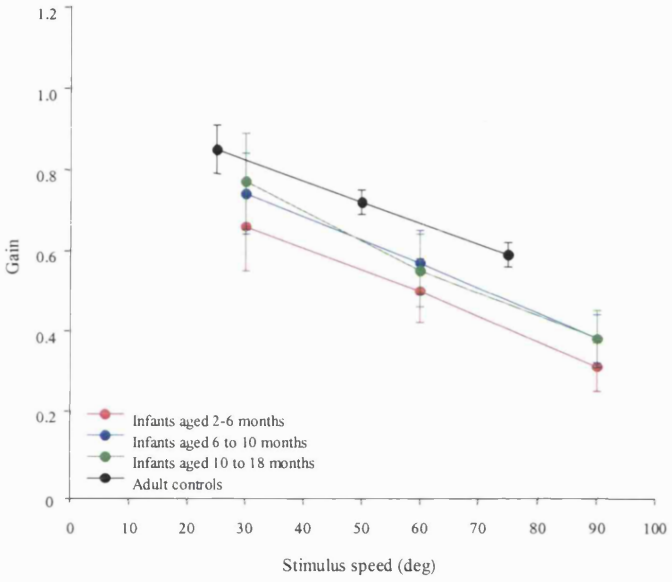


Figure 4.5. Slow phase velocity gain plotted against stimulus speed

Data collapsed across infants to form three age groups of 2 to 6 months (6 infants), 6 to 10 months (7 infants) and 10 to 18 months (5 infants). Error bars show ± 1 standard error of the mean of means.
Note, adult stimulus speeds were 25, 50 and 75°/s.

Table 4.1. Average slow phase velocity gains

		Stimulus velocity		
Infant	**Age***	**30°/s**	**60°/s**	**90°/s**
KK	18	0.91	0.69	0.29
FD	14.9	0.85	0.58	0.48
JT	13	0.73	0.55	0.43
PK	10.5	0.72	0.36	0.26
EA	10	0.62	0.56	0.44
TO	8.5	0.78	0.47	0.44
LC	8.2	0.74	0.71	0.57
KP	7.9	0.71	0.53	0.34
TM	7.5	0.76	0.66	0.27
AN	7.4	0.74	0.56	0.23
CA	6.5	0.75	0.48	0.45
EW	6	0.69	0.61	--
CH	5.9	0.72	0.57	0.45
NH	5.8	0.73	0.41	0.17
RG	4.4	0.69	0.62	0.29
ML	3.5	0.67	0.48	0.30
HW	2.8	0.57	0.34	0.32
SC	2.2	0.55	0.56	--
ADULT		**Stimulus velocity**		
CONTROLS		**25°/s**	**50°/s**	**75°/s**
		0.85 ± 0.06	0.72 ± 0.03	0.59 ± 0.03

Slow phase velocity gains at each stimulus speed. Data are means and pooled means (± standard error) for adult controls. *Age in months; --: insufficient data obtained.

4.2.4.3 Horizontal OKN quick phases

The quick phase beat frequency (rate of production per unit time) was calculated at each stimulus speed. Infants had a lower beat frequency compared to adult subjects (infants' mean beat frequency over all stimulus velocities = 1.1 ± 0.3 Hz; adults mean beat frequency over all stimulus velocities = 3.2 ± 0.3 Hz).

From each infant at least 200 quick phases were elicited during a recording session. Infants made quick phase amplitudes of up to 60°, whereas adults made very few quick phases above 30° (Figure 4.6).

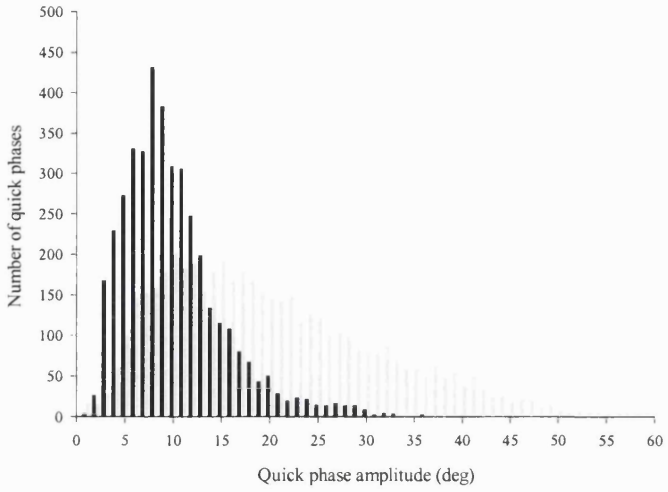


Figure 4.6. Horizontal OKN quick phase amplitudes

Histogram to show the distribution of amplitudes of all OKN quick phases elicited in this experiment.

Since adults rarely made quick phases greater than 30° we restricted our analysis of OKN quick phases to amplitudes between 4° (the point at which linearity of the adult main sequence for duration and peak velocity begins) and 30°. A reasonable number of quick phases were elicited across this range of amplitudes in both infants and adults (see Figure 4.6). Thus it was felt that a valid main sequence function had been obtained.

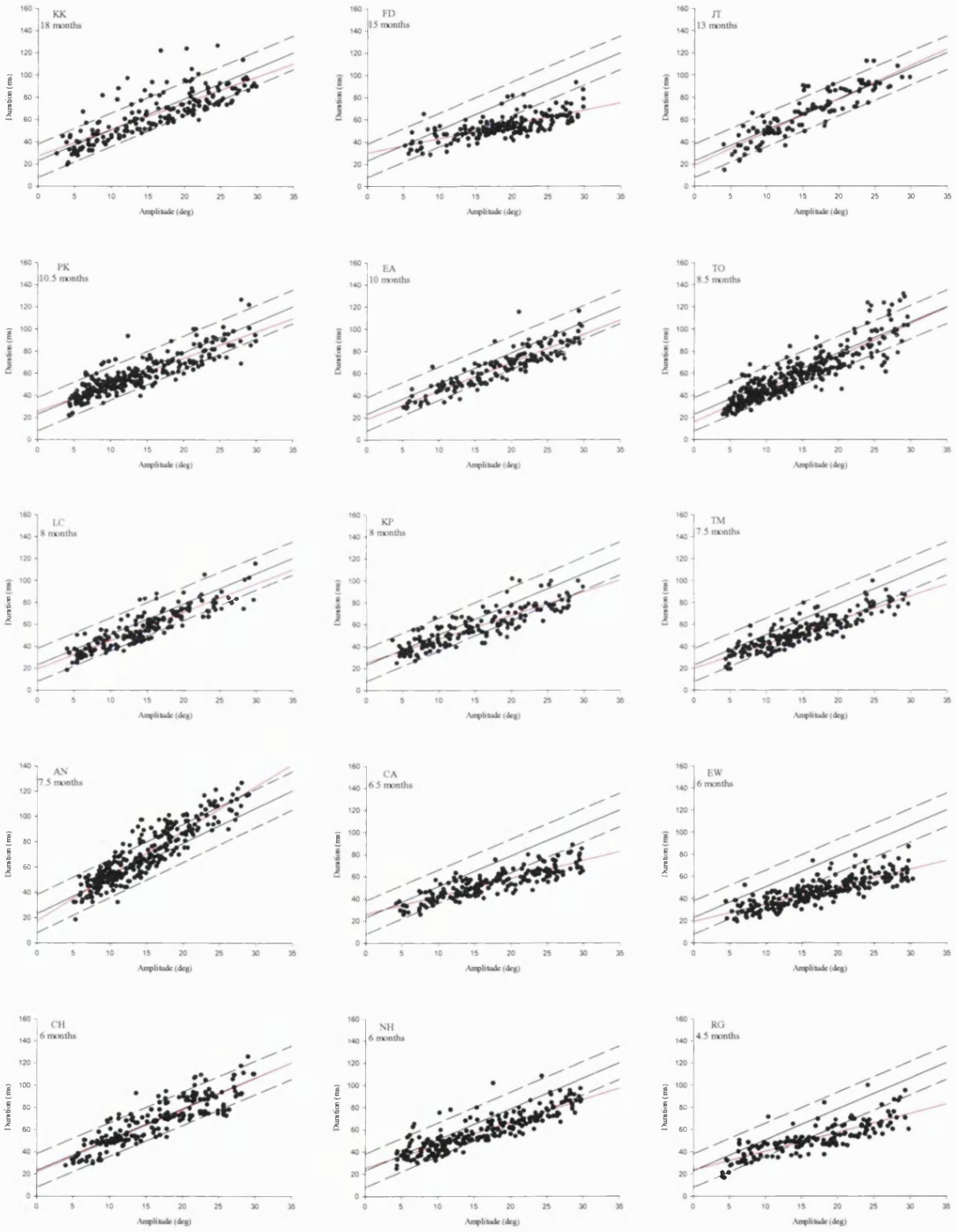
The main sequence for duration

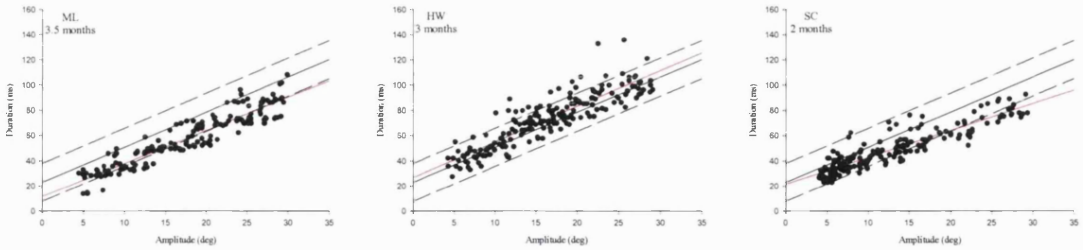
We plotted main sequences for duration (between 4 and 30°) for each infant and adult subject. These plots were fitted with a linear regression and the slope and intercept values are given in Table 4.2.

Figure 4.7 illustrates the main sequence for duration for each infant with 95% prediction intervals for adult controls. The infants' OKN quick phases often fell within the 95% prediction intervals for our adult controls. When the infants' OKN quick phases were not within the 95% prediction intervals of the adults they were usually faster – that is, they had a shorter duration.

Figure 4.7. Main sequence for duration for infants' quick phases

Scatter plots of OKN quick phase duration versus amplitude for each infant. Left and right eye movements are plotted together and only amplitudes between 4 and 30° are shown since this range was used for analysis. Dotted lines are 95% prediction intervals for adult control subjects. Red lines are linear regressions for infant quick phases. Continued overleaf.





For illustrative purposes we also plotted the main sequence for duration for *all* infant OKN quick phases and *all* adult OKN quick phases (Figure 4.8). The linear regression of the infants' OKN quick phases had a lower slope and slightly higher intercept compared to the regression of all the adults' OKN quick phases (infants' slope=2.26; intercept=23.22; r^2=0.61; adults' slope=2.72; intercept=22.88; r^2=0.72).

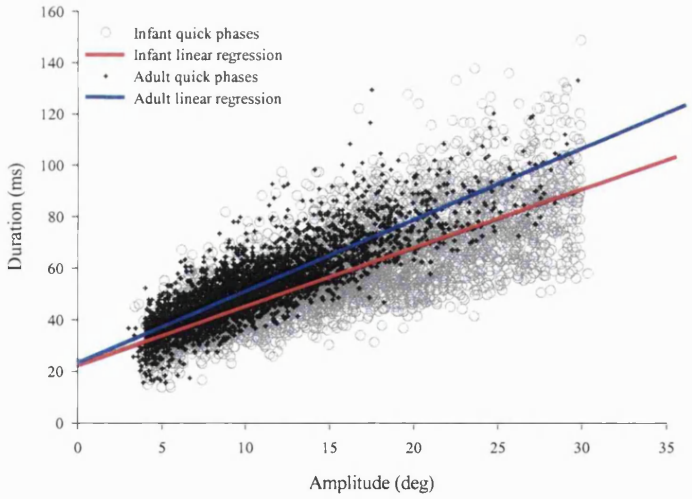


Figure 4.8. The OKN quick phase main sequence for duration for all subjects

Scatter plot of OKN quick phase duration versus amplitude (between 4 and 30°) for all infants and adult controls. Linear regression line for OKN quick phase amplitudes between 4 and 30° also shown.

To compare the main sequence parameters for duration of infants and adults statistically we used a multivariate analysis of variance (MANOVA), taking the slope and intercept of each individual main sequence as the dependent variables. This showed that for amplitudes between 4 and 30° the differences between infant and adult main sequences for duration were *not* significant (p=0.05, Hotellings T-test).

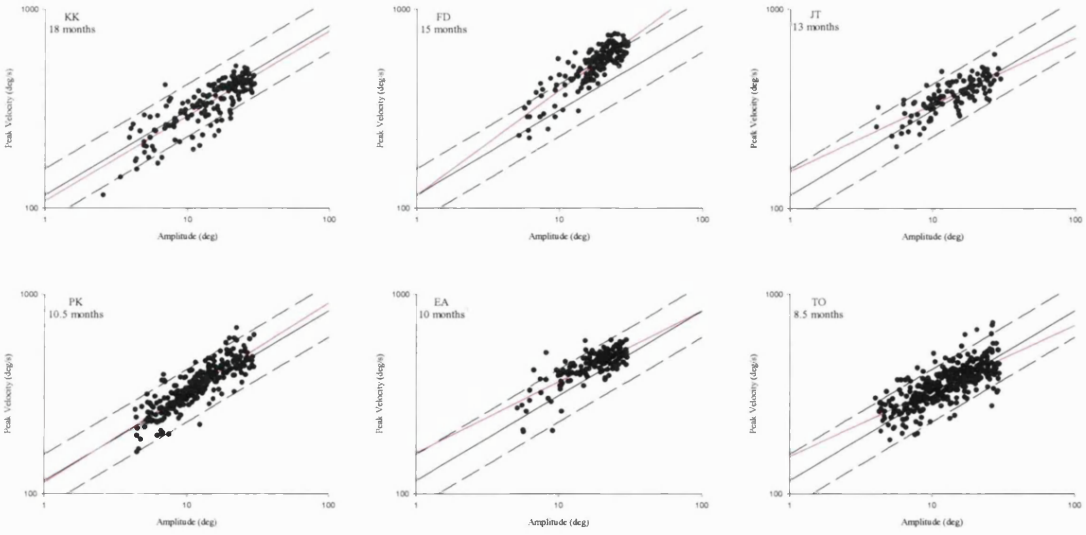
The main sequence for peak velocity

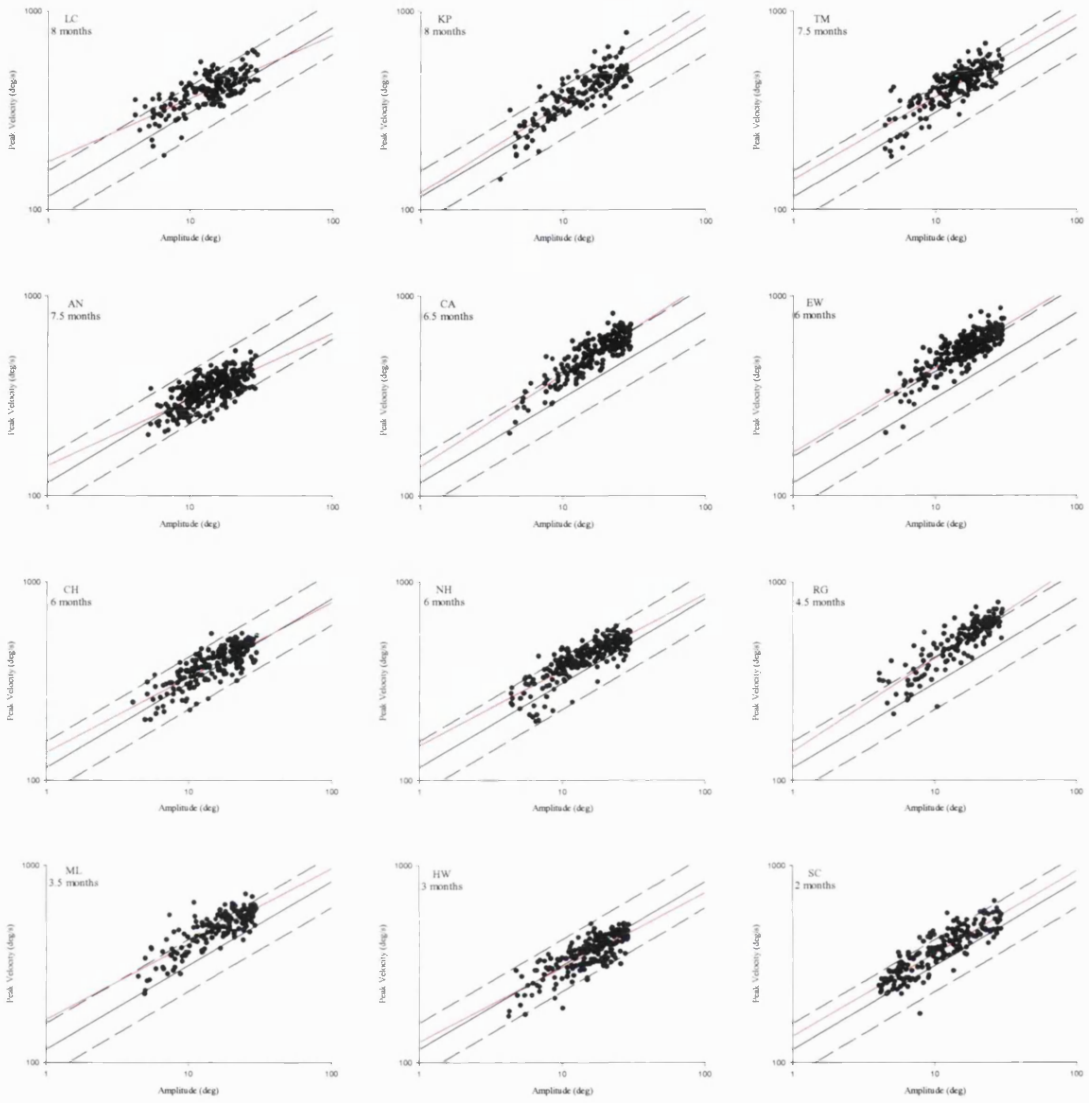
Since the relationship between OKN quick phase peak velocity and amplitude is not a linear one, we used a logarithmic (base 10) scale to plot peak velocity against amplitude (between 4 and 30°) for each infant and adult subject. These logarithmic plots were fitted with a linear regression and the slope and intercept values are given in Table 4.2.

Figure 4.9 illustrates the main sequence for peak velocity for each infant with 95% prediction intervals for adult controls. The infants' OKN quick phases frequently fell within the 95% prediction intervals for our adult controls. When the infants' OKN quick phases were not within the 95% prediction intervals of the adults they were usually faster – that is, they had a greater peak velocity.

Figure 4.9. The main sequence for peak velocity for infants' quick phases

Logarithmic plots of OKN quick phase peak velocity versus amplitude for each infant. Left and right eye movements are plotted together and only amplitudes between 4 and 30° are shown since this range was used for analysis. Dotted lines are 95% prediction intervals for adult control subjects. Red lines are linear regressions for infant quick phases. Continued overleaf.





For illustrative purposes we also constructed logarithmic plots of the peak velocity-amplitude relationship for *all* infant OKN quick phases and *all* adult OKN quick phases (Figure 4.10). When compared to the linear regression of the adults' main sequence for peak velocity the regression of the infants' main sequence for peak velocity had an identical slope but higher intercept (infants' slope=2.69; intercept=128.82; r^2=0.56; adults' slope=2.69; intercept=114.82; r^2=0.56).

Statistical testing, however, demonstrated that for amplitudes between 4 and 30° there was *no significant* difference between infant and adult main sequences for peak velocity (p=0.12, Hotellings T-test).

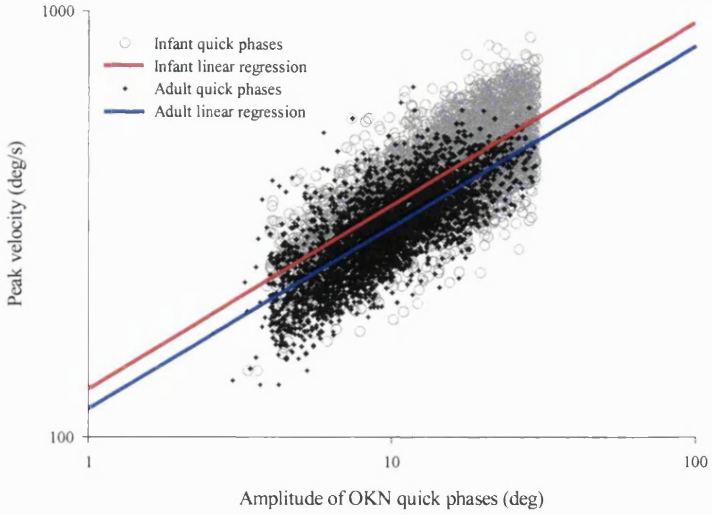


Figure 4.10. The OKN quick phase main sequence for peak velocity for all subjects

Logarithmic plot of OKN quick phase peak velocity versus amplitude (between 4 and 30°) for all infants and adult controls. Linear regression line for OKN quick phase amplitudes between 4 and 30° also shown.

Table 4.2. Main sequence parameters for OKN quick phases

		ALL QUICK PHASES >4°				QUICK PHASES 4-30°			
		D-A		PV-A		D-A		PV-A	
Infant	Age*	S	I	S	I	S	I	S	I
		ms/°	ms			ms/°	ms		
KK	18	2.46	26.32	0.36	2.10	2.41	27.30	0.43	2.04
FD	14.9	1.75	20.83	0.45	2.16	1.31	29.90	0.53	2.06
JT	13	3.14	17.23	0.34	2.22	3.04	18.92	0.32	2.19
PK	10.5	2.63	23.14	0.41	2.08	2.36	25.77	0.45	2.06
EA	10	2.63	17.58	0.32	2.24	2.58	18.51	0.36	2.20
TO	8.5	3.23	12.87	0.30	2.21	3.04	16.13	0.32	2.19
LC	8.2	3.04	14.67	0.28	2.28	2.57	19.35	0.32	2.24
KP	7.9	2.01	27.14	0.40	2.14	2.18	25.12	0.45	2.08
TM	7.5	2.35	16.65	0.34	2.22	2.15	20.21	0.41	2.15
AN	7.4	3.61	16.81	0.28	2.20	3.71	16.02	0.32	2.16
CA	6.5	1.59	25.56	0.38	2.23	1.63	25.83	0.43	2.06
EW	6	1.69	18.03	0.38	2.26	1.59	19.54	0.43	2.06
CH	5.9	2.62	24.45	0.36	2.16	2.77	22.94	0.38	2.14
NH	5.8	2.52	20.11	0.30	2.25	2.10	25.56	0.38	2.17
RG	4.4	2.17	15.72	0.38	2.24	1.73	23.55	0.48	2.15
ML	3.5	2.43	15.94	0.36	2.23	2.55	11.54	0.38	2.22
HW	2.8	2.62	30.35	0.34	2.14	2.79	26.73	0.38	2.10
SC	2.2	2.41	18.38	0.36	2.18	2.14	21.60	0.41	2.13
ADULT CONTROLS						2.37 ± 0.21	21.59 ± 1.33	0.42 ± 0.03	2.08 ± 0.04

The slope (S) and intercept (I) for the main sequence for the duration-amplitude relation were obtained from a linear regression of the main sequence for duration.
The slope (S) and intercept (I) values for the peak velocity-amplitude relation were obtained from a linear regression of the logged main sequence for peak velocity.
For adult subjects data are pooled means (± standard error). * Age in months.

4.2.5 Discussion

4.2.5.1 Saccades

Saccades were elicited for calibration purposes but the numbers were insufficient to draw any conclusions about the temporal characteristics of infants' saccades. However, we did show that hypometria is a robust phenomenon in normal infants. Even by 18 months of age occasional multiple hypometric saccades were present and thus accuracy had still not reached the level of the uninstructed adult. Therefore, it appears that development continues into later childhood.

In infants the multiple hypometric saccade sequences seen in eliciting saccade experiments have been interpreted as reflecting immaturities in the saccade-generating system (Aslin and Salapatek, 1975). However, they may reflect deficiencies in something other than the saccadic control system. Hainline and colleagues suggest that one possibility is an immaturity in the system responsible for spatial localisation of the target. Infants lack significant experience in spatial localisation, and consequently may be less able to localise small targets accurately in the absence of landmarks and contours (Hainline *et al.*, 1984b). An alternative suggestion put forward by these authors is that infant multiple hypometric sequences could be the result of an inattentive or drowsy state. In adult subjects multiple saccades and corrective saccades, which are larger than normal, increase with fatigue and reductions in arousal (Bahill and Stark, 1975; Abel *et al.*, 1983). However, the data we used was obtained when the infants were attentive and aroused but we still report that infants frequently make multiple hypometric saccades.

As reported in previous studies (Aslin and Salapatek, 1975; Salapatek *et al.*, 1980; Harris *et al.*, 1993a), we found that saccadic hypermetria is rare in infancy.

Thus, as with adults and older children, persistent hypermetria should be considered as abnormal. Saccadic hypermetria is often associated with cerebellar disease (Leigh and Zee, 1999). Cerebellar disorders can be difficult to detect in infancy, thus examining for saccadic hypermetria may be a worthwhile clinical investigation (Harris *et al.*, 1993a).

4.2.5.2 Slow phases of horizontal OKN

Overall, infants' horizontal OKN slow phases had lower frequency and gain, as well as higher amplitudes and longer durations than adult slow phases. Similar findings were reported by Hainline and Abramov (1995) for small-field horizontal and vertical OKN.

No slow build-up of OKN gain was present in the infants we tested. Even in the younger infants high gains were noted. This is strong evidence that we are measuring OKNe rather than OKNd. It seems, therefore, that infants possess an OKNe response, which is similar to that found in older children and adults. Since the infants tested were older than 2 months, it is possible that OKNe is not present in infants younger than this. However, Kremenitzer *et al.* (1979) did show an example of quite rapid build-up in the newborn, and Roy *et al.* (1989) reported high gains in the newborn. Therefore, it is possible that a functioning OKNe system is also present in the newborn. Thus, it is likely that the cortico-ponto-cerebellar pathway is functioning from an early age.

4.2.5.3 Quick phases of horizontal OKN

Typically infants' OKN had a beat frequency which was about a third of that of our adult subjects. It has been shown that the parameters of horizontal OKN depend on the subject's mental set. In "look" or "active" OKN subjects attend specific features of the OKN stimulus and exhibit OKN with high gain, high amplitude and low beat frequency. Whereas in "stare" or "passive" OKN subjects do not attend specific stimulus features and the OKN has a lower gain, lower amplitude, and higher beat frequency (Honrubia *et al.*, 1968). It is not possible to determine which type of OKN infants adopt. The low beat frequency and high slow phase amplitude in infant OKN could be interpreted as look-OKN. This was originally suggested by Schor (1990) but he has since argued that infant OKN is actually stare-OKN because of the presence of OKAN (Schor, 1993). Although attentional factors may be important, infants and young children may simply have higher thresholds (or longer latencies) for quick phases.

We found that there was very little difference in either the OKN quick phase main sequence for duration or the main sequence for peak velocity between infants and adults. Hainline *et al.* (1984a) reported that even in very young infants (less than 1 month of age) small-field OKN quick phases were saccadic like. However, the values given for the slope of the main sequence for peak velocity were lower in infants. Also when they plotted an infant's and adult's main sequence for peak velocity the infant clearly had slower quick phases. Their data, however, can not be directly compared to ours since they only considered the slope of the main sequence for peak velocity and not the intercept, the main sequence slopes were derived from data collapsed over orientation (horizontal and vertical quick phases combined) and

the amplitudes of the infants' quick phases did not exceed 10°. Moreover, only the quick phase peak velocity was taken into account and duration was not considered.

Hainline and Abramov (1995) and Hainline *et al.* (1984b) compared infant eye movements measured while subjects freely scanned visual stimuli. It was found that when viewing a textured stimulus, consisting of black and white gradient lines and patterns created from juxtaposed checkerboards of different check sizes, the slope of the main sequence for peak velocity of these fast eye movements were similar in infants and adults. However, when infants viewed simple geometric forms (circles, squares and triangles) saccades were slower.

We found no evidence for slow quick phases in infancy. Indeed, in our study, although the differences were not significant, infant OKN quick phases tended to be faster than adult quick phases.

Hainline *et al.* (1984b) felt that, when studying infant saccades, rather than requiring saccades on demand it is more appropriate to measure eye movements during free scanning of stimuli. We feel that it may be even more appropriate to use an optokinetic stimulus when studying infant saccades since, as shown in our study, a larger range of amplitudes are elicited. Also examination of the OKN slow phases provides further information about the state of the patient's oculomotor system.

4.3 Experiment 2: The horizontal OKN main sequence in a clinical population

4.3.1 Introduction

Slow saccades with a restriction of ocular motility usually indicate either abnormalities in the ocular motor periphery, such as ocular muscle or oculomotor nerve paresis, or lesions of the medial longitudinal fasciculus. Slow saccades occurring when the oculomotor range is full are usually caused by central neurological disorder. However, while it was originally believed that slow saccades due to central neurological disorders were pathognomonic of burst cell dysfunction, it is now known that disturbances of higher-level structures, including the cerebral hemispheres (Braun and Gault, 1969) and superior colliculus (Hikosaka and Wurtz, 1985), can also lead to slow saccades. It should be noted that drowsiness, inattentiveness, and drug intoxication have been shown to cause slow saccades (Jürgens *et al.*, 1981b; Thurston *et al.*, 1984) but, nevertheless, selective slowing of horizontal saccades usually indicate an abnormality in the pons.

Unless they are severe, slow saccades may not be obvious clinically. This is especially true in children. In young or sick children it is often not possible to elicit sufficient saccades to calculate the main sequence. However, in Chapter 3 we demonstrated that the main sequences of horizontal saccades and OKN quick phases are similar. Therefore, it would seem feasible to use the quick phases of OKN to estimate the saccadic main sequences because they are easier to elicit. However, before doing this we need to confirm that patients with abnormal saccades also have

abnormal OKN quick phases. To do this we examined children with Gaucher disease, a disease that is known to be associated with slow saccades.

Table 4.3. The aetiology of slow saccades

AETIOLOGY OF SLOW SACCADES
Spinocerebellar ataxias (SCA), especially SCA2 (olivopontocerebellar atrophy)
Huntington's disease
Progressive supranuclear palsy
Parkinson's (advanced cases) and related diseases; Lytico-Bodig
Whipple's disease
Lipid storage diseases
Wilson's disease
Drug intoxications: anticonvulsants, benzodiazepines
Tetanus
In dementia: Alzheimer's disease (stimulus-dependent), and in association with AIDS
Lesions of the paramedian pontine reticular formation
Internuclear ophthalmoplegia
Paraneoplastic syndromes
Amyotrophic lateral sclerosis (some cases)
Peripheral nerve palsy, diseases affecting the neuromuscular junction and extraocular muscle, restrictive ophthalmopathy

From Leigh and Zee, 1999

Gaucher disease (GD) is an autosomal recessively inherited lysosomal storage disorder. It is characterised by deficient activity of the lysosomal enzyme ß-glucosidase, resulting in the accumulation of its substrate, glucosylceramide. This leads to multi-system disease involving enlargement and dysfunction of the spleen and liver, destruction of bone, and in severe cases pulmonary infiltration. In some patients there is also involvement of the central nervous system (CNS) (Beutler and Grabowski, 1995) which has led to the traditional sub-typing of GD into the following groups: GD1 (non-neuronopathic) in which there is an absence of CNS involvement; GD2 (acute infantile) in which there is a rapid neurological progression leading to death, usually by 2 years of age; GD3 (subacute neuronopathic) in which there is a

slower and more variable neurological progression. It is essential to differentiate between the different subtypes since patients with GD3 require a higher dose of enzyme replacement therapy to slow down the neurological progression of the disease. In the early stages it is not easy to clinically differentiate between GD1 and GD3 as neurological signs, which are not present in GD1 but are present in GD3, may be subtle. However, eye movement recordings may identify neurological involvement early on, aiding the correct diagnosis and indicating high-dose treatment.

The most consistent oculomotor sign of GD2 and GD3 is saccade initiation failure ('ocular motor apraxia') and this is also often the first sign of neurological involvement. Harris and colleagues (1999) investigated the ocular motor abnormalities of six children with GD3. All of these children demonstrated horizontal saccade initiation failure (HSIF). Horizontal saccades were assessed quantitatively in four of the children, and in all four these were grossly slow. In the remaining two children it was not possible to assess saccades quantitatively but clinically they were judged to be slow. In the presence of otherwise normal motility and range these slow saccades were considered to be due to lesion(s) in the supranuclear saccade centres of the brainstem. In the one case of GD1 that was assessed by Harris *et al.* (1999) saccades were of normal speed.

The aim of this experiment was to determine if, like saccades, OKN quick phases are slower in patients with GD3 but normal in GD1. If this is the case it would be feasible to use OKN testing as a clinical tool to identify abnormally slow saccades.

4.3.2 Methodology

Five children with GD3 (neuronopathic) and five children with GD1 (non-neuronopathic) were studied. There were seven girls and three boys with an age range

of 5 to 17 years. Ten control subjects with an age range of 5-21 years, none of whom had any known neurological disorder, were also studied. Informed consent was obtained from the parents of the younger children and from the older subjects themselves.

Horizontal eye movements were recorded using bi-temporal EOG. The full-field curtain and protocol described in 4.2.3.4 was used to elicit horizontal OKN. Older children sat alone, younger children sat on a parent's lap. The head was immobilised by a chin rest or was held by a parent or the examiner.

Saccades were used for calibration. These were elicited to red LEDs placed at pre-set calibrated positions 10^{o} to the left and right of centre. Between ten and twenty saccades were elicited or as many as co-operation allowed.

The computer program described in Chapter 2 was used for analysis. However, because in some cases quick phases were very slow, the threshold for peak velocity detection was reduced to 10°/s. Main sequences for duration and logged (base 10) peak velocity were plotted. These were fitted with regression lines, and the slope and intercept values for the patients were compared to the control subjects.

4.3.3 Results

All five GD3 children had HSIF and, therefore, intermittently missed quick phases during induced horizontal OKN (Figure 4.13a). Thus, compared to the controls relatively fewer OKN quick phases could be recorded from the patients.

Compared to the control subjects GD3 children had slow OKN quick phases (i.e. quick phases of increased duration and decreased peak velocity) (Figure 4.11a, 4.12a). Statistical analysis demonstrated that the differences in the duration and in the peak velocity were highly significant ($p<0.001$, Hotellings T-test).

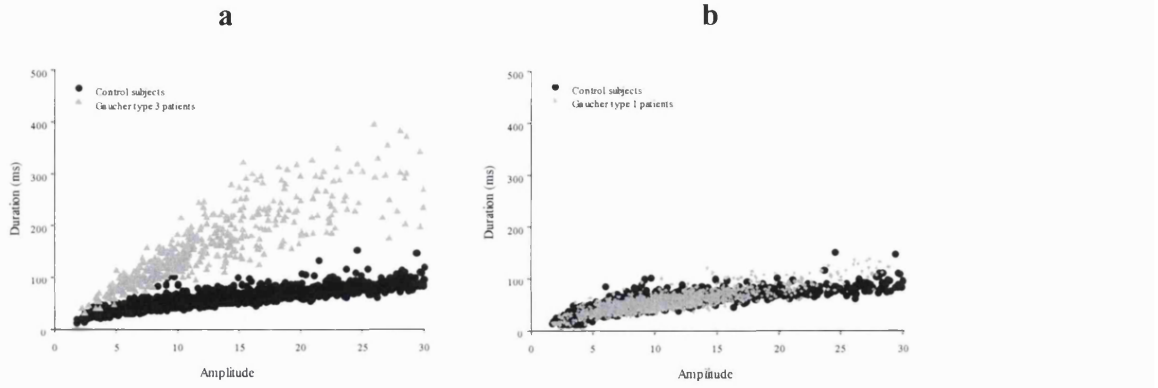
Children with GD1 did not have HSIF (Figure 4.13b). No significant differences were found in the duration (p=0.13, Hotellings T-test) or in the peak velocity (p=0.68, Hotellings T-test) of OKN quick phases between the group of GD1 children and the control subjects (Figure 4.11b, 4.12b).

Table 4.4 The main sequence for duration - Gaucher patients and control subjects

			Gaucher patients		Control subjects	
Patient	Status	Age (years)	S ms/°	I ms	S ms/°	I ms
SY	GD3	12	9.06	56.80	2.27	30.28
DB	GD3	11	9.28	72.35	1.72	32.99
SS	GD3	11	8.15	55.68	2.19	33.63
MC	GD3	5	9.56	73.97	2.00	32.27
NF	GD3	5	9.31	36.24	3.12	26.23
EW	GD1	17	2.38	24.82	1.73	30.10
BL	GD1	12	2.72	25.61	3.36	27.44
NO	GD1	11	2.91	29.43	2.42	28.09
KG	GD1	8	3.42	22.68	1.84	32.16
CG	GD1	5	3.40	24.48	1.64	40.76

The slope (S) and intercept (I) values were obtained from a linear regression of the main sequence for duration for OKN quick phase amplitudes >4°.

Figure 4.11. The OKN main sequence for duration - Gaucher patients and control subjects



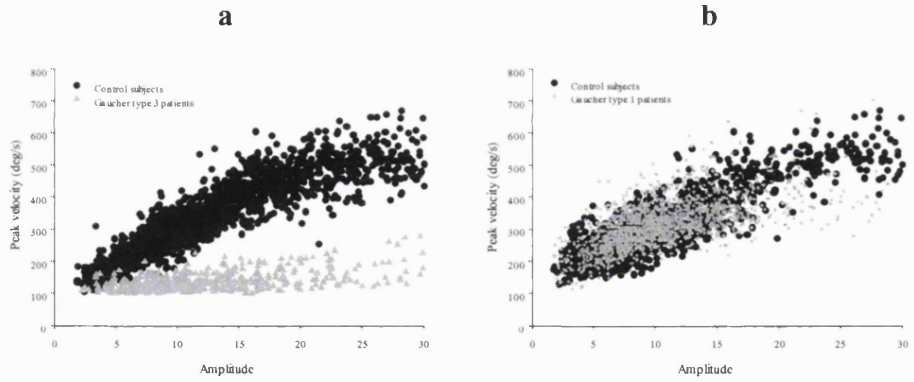
The OKN main sequence for duration for (a) five Gaucher type 3 patients and five control subjects and (b) five Gaucher type 1 patients and five control subjects.

Table 4.5 The main sequence for peak velocity - Gaucher patients and control subjects

			Gaucher patients		Control subjects	
Patient	Status	Age (years)	S	I	S	I
SY	GD3	12	0.47	1.58	0.43	2.08
DB	GD3	11	0.39	1.63	0.54	1.98
SS	GD3	11	0.34	1.78	0.62	1.83
MC	GD3	5	0.29	1.74	0.44	2.08
NF	GD3	5	0.34	1.80	0.55	1.90
EW	GD1	17	0.52	1.97	0.53	1.98
BL	GD I	12	0.53	1.97	0.37	2.12
NO	GD1	11	0.42	2.13	0.40	2.13
KG	GD1	8	0.37	2.08	0.58	1.93
CG	GD1	5	0.30	2.25	0.55	1.95

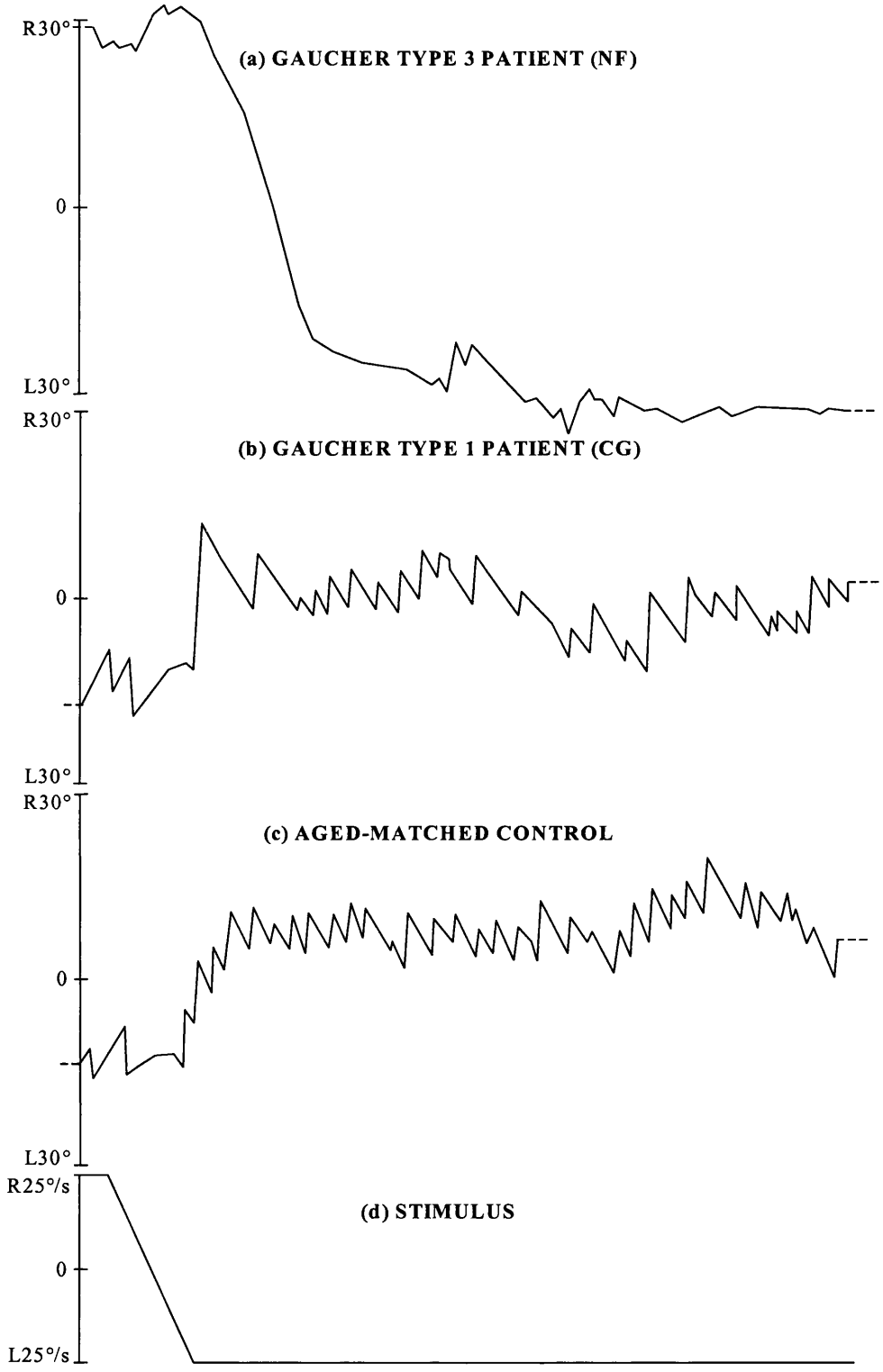
The slope (S) and intercept (I) values were obtained from a linear regression of the logged main sequence for peak velocity for quick phase amplitudes > 4°.

Figure 4.12. The OKN main sequence for peak velocity - Gaucher patients and control subjects



The OKN main sequence for peak velocity for (a) five Gaucher type 3 patients and five control subjects and (b) five Gaucher type 1 patients and five control subject

Figure 4.13. Extracts of horizontal OKN



Extract of horizontal OKN recorded from (a) a child with Gaucher disease type 3 (NF), (b) a child with Gaucher disease type 1 (CG) and (c) an aged-matched control. (d) The curtain was moving at an angular speed of 25°/s initially rightward then leftward in all traces. Stimulus acceleration was $20°/s^2$. Note the patient with Gaucher type 3 has a horizontal saccade initiation failure and therefore the eyes deviate to the mechanical limit of gaze in the direction of stimulus motion.

4.3.4 Discussion

All the patients with GD3 had HSIF and qualitatively they all appeared to have slow horizontal saccades. In this study the OKN quick phases of all the children with GD3 had longer durations and lower peak velocities compared to the control subjects. Thus, it appears that in GD3 horizontal OKN quick phases, like saccades, are slow.

None of the GD1 patients had HSIF, nor did they appeared to have slow saccades clinically or indeed any other signs of neurological involvement. We found no significant differences in the duration or peak velocity of horizontal OKN quick phases between GD1 children and the control subjects. Thus it appears that horizontal OKN quick phases, like saccades, are not affected in GD1 and this is consistent with their diagnosis of non-neuronopathic disease.

Slow saccades in the presence of otherwise normal motility and range are most commonly due to lesions in the supranuclear saccade centres (Leigh and Zee, 1999). For horizontal saccades these lie in the paramedian pontine reticular formation of the tegmentum. This is consistent with the post-mortem findings of a GD case with abnormal saccades. Büttner-Ennever *et al.* (1988) reported dense gliosis of the tegmental raphe, and suggested disruption of pause neurons and the crossing axons of inhibitory burst units which are essential for the generation of horizontal saccades.

4.4 Conclusion

The first experiment in this chapter compared the temporal characteristics of infant horizontal OKN quick phases with those of adults. Infants aged between 2 and 18 months were examined in a cross-sectional study. We found that the speeds of

infant and adult horizontal OKN quick phases are very similar. Thus, we can assume that the horizontal saccades in both infants and adults are also very similar. Therefore, although multiple hypometria demonstrates that infant saccades are immature, they are not slow as has previously been suggested (Hainline *et al.*, 1984b; Hainline and Abramov, 1995). Slow OKN quick phases and saccades should always be considered as abnormal, even in infants as young as 2 months.

The second experiment compared horizontal OKN quick phases elicited from five subjects with Gaucher disease type 3 (neuronopathic) and five subjects with Gaucher disease type 1 (non-neuronopathic) with two groups of five control subjects. Compared to the control subjects, the horizontal OKN quick phases elicited from the children with Gaucher disease type 3 had a significantly increased duration and a lower peak velocity. The quick phases elicited from the children with Gaucher disease type 1 were not significantly different from control subjects. All the children with Gaucher disease type 3 had horizontal saccade initiation failure indicating that they had brainstem involvement. Although further clinical studies are needed, our study suggests that the use of horizontal OKN quick phases to determine a main sequence for duration and for peak velocity is a useful clinical tool for identifying brainstem pathology. OKN is an involuntary response that is easily elicited, and so the greatest use of this technique would be in young or unco-operative patients. Also, the simplicity of OKN testing would permit serial recordings giving objective measurement of disease progression. Furthermore, this technique gives us the opportunity to determine the full range of conditions associated with abnormal saccades in infants and children.

Chapter 5 - Gaze Position during Horizontal Optokinetic Nystagmus

5.1 Introduction

In the previous experiments we noted that the quick phases of horizontal OKN did not only return the eyes to the centre of the orbit, but also directed them beyond the primary position. We will refer to this as "contraversion". Thus, during full-field OKN, the mean position of gaze was shifted in the direction of the quick phases i.e. in the opposite direction to stimulus movement and into the part of the visual field from which the motion originated. This phenomenon has previously been reported to occur in man (Jung and Mittermaier, 1939; Miyoshi *et al.*, 1978; Dubois and Collewijn, 1979a; Abadi *et al.*, 1999; Thilo *et al.*, 2000; Watanabe, 2001), in monkeys (Kubo *et al.*, 1981), in cats (Schweigart and Hoffmann, 1988; Schweigart, 1995) and in rats (Meier and Dieringer, 1993; Bähring *et al.*, 1994). A similar shift in the position of gaze has also been observed during vestibular nystagmus. It has been reported that the mean eye position of vestibular nystagmus shifts in the direction of head rotation (Melvill-Jones, 1964; Chun and Robinson, 1978; Roucoux *et al.*, 1981; Vidal *et al.*, 1982; Crommelinck *et al.*, 1982; Siegler *et al.*, 1998).

Although recognised as an oculomotor phenomenon, contraversion is poorly understood. It has been suggested that it might be a strategy for directing the line of sight into the visual field from which motion is originating (Abadi *et al.*, 1999; Thilo *et al.*, 2000; Watanabe, 2001). In this theory it is proposed that the quick phases strategically re-orient the eyes in the direction of self-motion so that the visual system

can detect a target more efficiently in the visual field toward which the head and/or body is moving.

In our study we examined contraversion in healthy adults and defined this phenomenon over a range of stimulus speeds including very low ones. We also examined a child with absent smooth pursuit and a leaky eye position integrator, as we had previously observed extreme contraversion in other patients with this disorder (Harris *et al.*, 1993b).

5.2 Preliminary study

The purpose of the preliminary study was to determine the most appropriate stimulus velocities for studying the shift in gaze position during full-field horizontal OKN.

5.2.1. Methodology

5.2.1.1 Subjects and recording methods

Five healthy adult volunteers (two males, three females) aged between 23 and 28 years participated in the preliminary study. None had a history of strabismus or had any known neurological or oculomotor problems. Informed consent was obtained from all subjects.

Horizontal eye movements were recorded using bi-temporal EOG. The subject's head was supported by a chin rest and the importance of keeping still was stressed. Alertness was maintained by frequent verbal encouragement.

5.2.1.2 Visual stimuli

A full-field, brightly coloured, richly patterned curtain was used as the horizontal optokinetic stimulus (see Chapter 2). This curtain was rotated rightward and leftward at various speeds. Each step of optokinetic stimulation lasted 20s followed by a 10s fixation period. A red LED light in the primary position was used as a fixation target. This was placed 75 cm from the subject and was viewed in darkness.

5.2.1.3 Procedure

The subject, in the dark, started by fixating for 10s the fixation target. Meanwhile, the OKN curtain was set to rotate at a constant velocity, randomly chosen out of five different values (10, 20, 30, 40 and 50°/s); the direction of the stimulus (rightward or leftward) was also randomised. At the end of the fixation period, the fixation target was automatically switched off and the curtain was illuminated for 20s. After every optokinetic stimulation period, the background light was switched off and the fixation target turned back on. During optokinetic stimulation subjects were instructed to keep the curtain as clear as possible but not to track any individual feature. During fixation they were instructed to look at the red light and to try to avoid blinking.

5.2.1.4 Data analysis

The analysis program in Chapter 2 was used to determine the start and the end of each OKN quick phase and calculate its midpoint. Each midpoint value was

subtracted from the primary gaze position prior to stimulus onset and the mean gaze position was then determined for every stimulus speed and each direction by taking an average of these values.

5.2.2 Results

With respect to primary gaze, optokinetic stimulation at all velocities led to a deviation of mean gaze position in the direction opposite to stimulus motion (Figure 5.1). There was a tendency for eccentric gaze position to increase with increasing stimulus velocity, but this increase was not significant. Over all the subjects and all the velocities tested, mean gaze position shifted between 3.15 and 26.41° in the direction contrary to stimulus motion. Individual gaze position values are listed in Table 5.1.

Table 5.1. Preliminary study - Mean horizontal gaze position

		Stimulus Velocity (°/s)				
		10	**20**	**30**	**40**	**50**
AH	**R**	23.92	16.23	17.57	26.41	25.58
	L	18.69	16.29	20.74	18.62	19.64
AW	**R**	3.15	9.90	10.65	7.86	8.74
	L	14.95	20.40	13.69	11.38	17.87
MH	**R**	6.62	15.92	9.87	12.65	10.94
	L	7.49	8.40	8.42	9.10	18.98
RH	**R**	6.83	7.24	8.23	2.83	5.21
	L	5.70	10.34	12.18	17.79	15.67
SG	**R**	13.10	9.47	17.13	14.92	14.68
	L	16.68	18.68	21.43	18.15	19.99
All subjects		**11.71 ± 2.14**	**13.29 ± 1.49**	**13.99 ± 1.56**	**13.97 ± 2.12**	**15.73 ± 1.91**

Mean horizontal gaze position during OKN at all stimulus velocities recorded by EOG. Values are normalised with respect to the direction of the optokinetic curtain so that positive values indicate a deviation in the direction opposite to curtain rotation. Pooled average (mean ± standard error) of mean gaze position for all subjects at each stimulus velocity (rightward and leftward curtain direction combined) also shown. R: rightward curtain rotation; L: leftward curtain rotation.

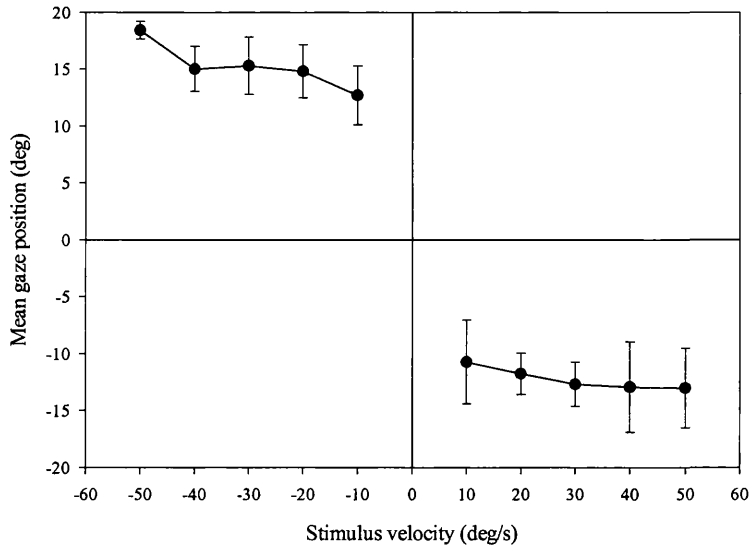


Figure 5.1. Preliminary experiment - Mean horizontal eye position

Pooled means and standard errors of horizontal eye position at a range of optokinetic stimulation velocities. Negative values represent movements to the left.

5.3 Main study

In the follow-up to our preliminary study, we investigated further the effect of stimulus velocity on the position of gaze during optokinetic stimulation. This study was done using the more accurate infrared reflection technique. This technique has a more restricted horizontal linear range but it has a much higher resolution than EOG and, thus, enabled a more exact measurement of gaze position. Furthermore, unlike EOG, the infrared reflection technique is not subject to drift. Drift could bias the measurement of gaze position.

The preliminary study demonstrated that if stimulus velocity was below 30°/s the eyes did not exceed the linear range (± 25°) of the infrared eye tracker. Thus, in our main experiment we chose to use stimulus velocities between 2 and 30°/s, in steps of 2°/s. Nevertheless, an EOG recording was taken throughout the experiment to verify that eye movements did indeed stay within the range of the eye tracker.

5.3.1. Methodology

5.3.1.1 Subjects and recording methods

OKN was recorded from ten healthy adults (four males, six females) aged between 22 and 31 years. None had a history of strabismus or had any known neurological or oculomotor problems.

An affected child from a family with a dominant vestibulocerebellar disorder (Harris *et al.*, 1993b) [OMIM#193003] also participated in the experiment. Informed consent was obtained from all subjects, and the parents of the child, after the nature of the study had been explained.

The adult subjects horizontal eye movements were recorded using an infrared eye tracker and EOG simultaneously. The eye movements of the child were recorded using only EOG.

5.3.1.2 Visual stimuli and procedure

The optokinetic curtain, fixation target and procedure were the same as in the preliminary experiment. However, fifteen stimulus velocities were used (2-30°/s, in increments of 2°/s).

The child with the vestibulocerebellar disorder also underwent additional oculomotor tests. Smooth pursuit was tested by ramping a large target horizontally at a constant speed of 10, 20, 30, and 40°/s, through a total angle of 40° symmetrically about the midline. There was a 1.5s pause at the end of each excursion. The time constant of the horizontal neural integrator was estimated from the centripetal drift during eccentric fixation in the dark.

5.3.1.4 Data analysis

The analysis was as described in 5.2.1.4. However, we also calculated the velocity of each slow phase to determine OKN slow phase velocity gains (see Chapter 2).

5.3.2. Results – Normal Controls

5.3.2.1 Slow phase velocity gain

As can be seen in Figure 5.2, slow phase velocity gain decreased with increasing stimulus velocity. The greatest decrease in gain occurred between 2°/s and 10°/s, thereafter there was a more gradual decrease. Table 5.2 gives detailed listings of slow phase gain values obtained at the different stimulus velocities.

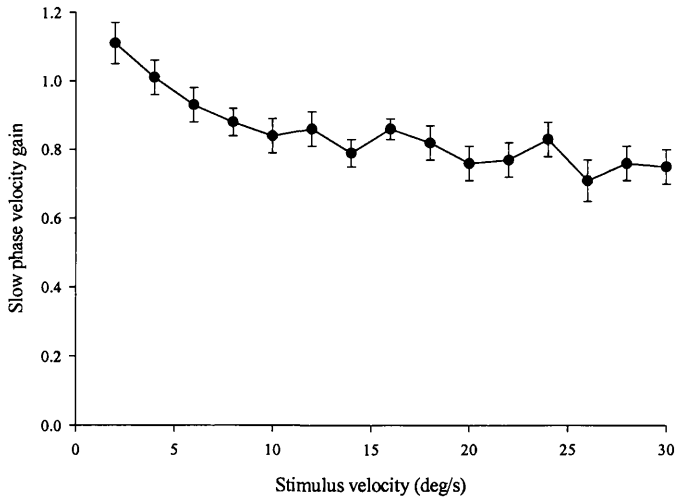


Figure 5.2. Horizontal slow phase velocity gain

Pooled mean and standard errors of horizontal OKN slow phase velocity gain.

Table 5.2. Horizontal OKN slow phase velocity gain

		Stimulus velocity (°/s)														
Subj	**Dir**	**2**	**4**	**6**	**8**	**10**	**12**	**14**	**16**	**18**	**20**	**22**	**24**	**26**	**28**	**30**
AH	R	1.51	0.92	0.55	1.05	0.63	0.44	0.91	0.63	0.67	0.49	0.75	0.44	0.45	0.45	0.40
	L	1.54	1.38	0.93	1.13	1.16	1.00	0.52	0.83	0.63	0.94	0.45	1.06	0.89	0.90	0.75
AW	R	1.22	1.04	1.01	0.86	0.79	0.69	0.99	0.90	0.96	0.91	0.89	0.91	0.89	0.76	0.86
	L	0.87	1.13	1.05	0.96	1.13	1.05	1.04	0.98	0.91	1.07	1.03	1.01	1.03	1.03	0.98
LG	R	1.42	1.24	1.09	0.74	0.84	0.85	0.91	0.88	0.79	0.72	0.84	0.80	0.63	0.79	0.66
	L	0.47	0.87	0.72	0.79	0.89	0.93	0.95	0.76	0.70	0.78	0.84	0.77	0.91	0.94	0.82
LP	R	1.02	0.87	0.91	0.94	0.64	1.01	0.63	0.67	0.73	0.68	0.66	0.94	0.60	0.64	0.82
	L	1.11	0.84	1.13	0.78	1.01	1.34	0.65	0.86	1.04	0.77	0.81	0.94	0.70	0.78	0.90
MH	R	0.85	0.80	0.85	0.66	0.55	0.61	0.52	0.62	0.51	0.56	0.48	0.68	0.47	0.51	0.54
	L	0.66	0.54	0.54	0.53	0.37	0.51	0.47	0.51	0.34	0.46	0.31	0.45	0.44	0.46	0.44
NC	R	1.13	0.98	1.02	0.84	0.67	0.88	0.97	0.86	0.90	0.74	0.91	0.82	0.88	0.82	0.88
	L	1.00	1.01	0.98	0.92	0.93	0.85	0.91	0.86	0.87	1.00	0.97	0.88	0.79	0.56	0.79
PC	R	1.17	1.13	0.89	1.04	0.92	0.75	0.55	0.98	0.68	0.65	0.56	0.57	0.88	0.68	0.47
	L	1.37	0.90	0.99	0.66	0.96	0.60	0.81	1.07	0.91	0.58	0.76	1.03	0.42	0.95	0.72
PI	R	1.32	1.09	0.92	0.82	0.62	0.93	0.75	0.85	0.73	0.53	0.70	0.70	0.57	0.67	0.65
	L	1.25	1.11	1.12	1.20	1.20	1.14	1.07	1.03	1.13	1.09	1.18	1.09	1.08	1.11	1.10
RH	R	1.09	1.34	1.26	1.09	1.14	1.05	0.98	1.05	1.13	1.05	1.07	1.02	1.00	1.02	1.02
	L	1.08	0.84	0.71	0.76	0.63	0.75	0.63	0.86	0.82	0.57	0.60	0.60	0.32	0.51	0.58
SG	R	1.09	1.34	1.26	1.09	1.14	1.05	0.98	1.05	1.13	1.05	1.07	1.02	1.00	1.02	1.02
	L	1.08	0.84	0.71	0.76	0.63	0.75	0.63	0.86	0.82	0.57	0.60	0.60	0.32	0.51	0.58
ALL SUBJECTS		**1.11 ± 0.06**	**1.01 ± 0.05**	**0.93 ± 0.05**	**0.88 ± 0.04**	**0.84 ± 0.05**	**0.86 ± 0.05**	**0.79 ± 0.04**	**0.86 ± 0.03**	**0.82 ± 0.05**	**0.76 ± 0.05**	**0.77 ± 0.05**	**0.83 ± 0.05**	**0.71 ± 0.06**	**0.76 ± 0.05**	**0.75 ± 0.05**

Mean horizontal optokinetic slow phase velocity gain for each subject at each stimulus speed. Recorded using the infrared eye tracker. Average (mean ± standard error) of mean slow phase velocity for all subjects (rightward and leftward curtain rotation combined) at each stimulus velocity are also shown. Dir: curtain direction; R: rightward rotation; L: leftward rotation

5.3.2.2 Gaze position

Even at very low stimulus speeds, the mean gaze always shifted in the direction of the quick phase. Inter-individual differences in the mean gaze shift were large. In some subjects there were also large differences in the mean gaze shift during rightward stimulation compared to the mean gaze shift during leftward stimulation.

Over all subjects and all velocities tested, mean gaze position shifted between 0.34 and 26.43° (average = 10.64°, standard error = 0.32) in the direction contrary to stimulus motion. In normals, contraversion was *not* all-or-none but showed a significant increase with stimulus velocity up to 10°/s ($p<0.05$, for the averaged data from all subjects). At higher stimulus velocities there was no significant increase in contraversion (Figure 5.3). To confirm that the saturation was not due to the limited linear range of the infrared eye tracker we compared the results to those recorded by EOG. The mean gaze shift recorded by EOG was not significantly different to that recorded by the eye tracker (Figure 5.3).

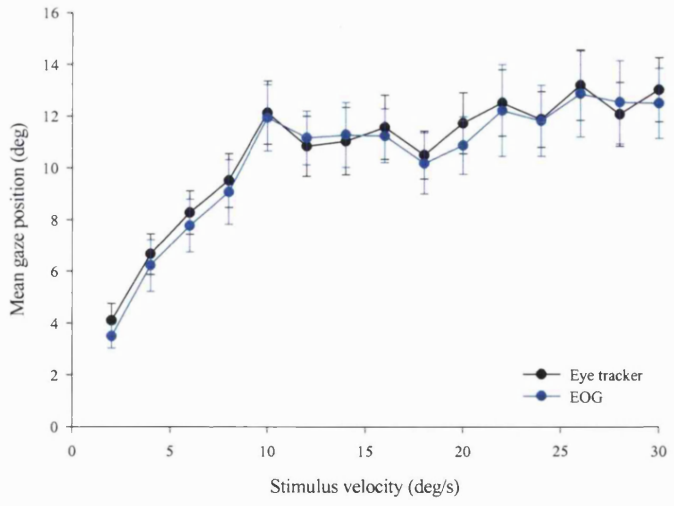


Figure 5.3. Gaze position during horizontal OKN

Pooled means and standard errors of horizontal gaze position at each stimulus velocity (rightward and leftward stimulus rotation combined).
Eye position values are normalised according to the direction of stimulus motion with positive values denoting a deviation from primary gaze in the direction opposite to stimulus motion.
Data recorded by the infrared eye tracker and by EOG shown.

Table 5.3 Horizontal gaze position during OKN

		Stimulus velocity (°/s)														
Subject	**Dir**	**2**	**4**	**6**	**8**	**10**	**12**	**14**	**16**	**18**	**20**	**22**	**24**	**26**	**28**	**30**
AH	R	5.73	5.62	10.65	13.49	18.58	14.80	17.07	12.13	10.86	9.62	22.45	11.81	21.52	11.04	12.97
	L	1.14	10.90	4.12	7.65	20.63	21.80	18.60	7.64	6.40	10.46	13.14	13.68	9.50	14.06	19.19
AW	R	1.60	2.20	4.42	3.45	5.73	5.52	7.92	6.99	14.51	6.51	6.12	7.74	8.26	4.83	7.46
	L	7.11	11.22	13.55	16.18	19.37	16.36	14.96	18.30	14.71	20.20	17.66	17.18	12.45	14.10	18.06
LG	R	5.95	8.92	9.58	9.79	10.11	9.53	6.70	14.75	8.23	8.07	12.06	5.08	12.16	11.01	11.53
	L	3.98	5.41	5.68	5.81	5.59	6.09	6.12	8.99	11.47	12.73	9.85	12.03	10.93	8.96	13.19
LP	R	2.25	4.27	11.42	10.93	14.78	16.46	19.17	15.69	14.68	12.22	20.52	17.37	15.54	17.20	18.23
	L	4.81	10.84	8.57	16.38	20.27	12.19	17.50	25.39	14.18	21.85	20.91	18.98	24.08	19.98	23.44
MH	R	3.53	2.05	3.49	4.48	5.41	3.60	4.71	7.76	6.25	6.44	6.14	2.87	7.91	6.98	7.73
	L	3.44	1.59	4.77	5.88	5.61	4.30	5.42	6.17	5.92	7.21	8.45	10.39	6.57	8.23	9.47
NC	R	0.34	3.71	3.40	7.61	6.78	6.95	3.97	4.53	7.79	5.31	6.89	6.38	4.16	7.64	6.50
	L	5.22	10.72	9.10	14.82	11.68	8.90	15.23	17.06	14.10	15.42	19.38	14.07	17.04	15.04	20.31
PC	R	3.30	4.90	5.71	7.48	11.65	9.12	3.92	10.02	11.63	12.56	5.75	12.07	12.43	8.07	8.73
	L	2.59	3.07	4.42	3.71	7.43	5.60	6.29	6.84	7.17	4.72	6.86	7.94	6.47	8.68	8.67
PI	R	10.15	4.79	8.37	12.1	9.95	6.81	4.79	10.62	7.14	9.58	10.22	11.26	12.10	10.73	9.87
	L	9.87	7.10	10.15	10.49	13.73	16.15	8.37	12.25	10.22	18.73	11.26	10.62	17.73	18.73	8.57
RH	R	0.91	4.88	12.48	7.87	7.57	9.37	10.93	4.18	5.73	7.42	8.24	8.42	5.71	4.33	6.07
	L	7.31	12.32	12.03	11.53	12.42	10.12	12.30	8.39	8.22	13.47	10.17	15.69	16.31	11.98	11.42
SG	R	1.33	7.40	7.00	10.74	15.60	15.71	17.88	14.97	9.43	11.53	13.75	11.73	18.28	13.49	17.04
	L	1.45	11.32	16.59	20.9	19.66	17.37	18.87	18.74	21.38	20.46	20.50	22.07	24.81	26.43	22.13
ALL SUBJECTS		**4.10 ± 0.65**	**6.66 ± 0.79**	**8.28 ± 0.84**	**10.06 ± 1.04**	**12.13 ± 1.22**	**10.84 ± 1.16**	**11.04 ± 1.30**	**11.57 ± 1.24**	**10.50 ± 0.92**	**11.73 ± 1.18**	**12.52 ± 1.28**	**11.87 ± 1.08**	**13.20 ± 1.36**	**12.08 ± 1.23**	**13.03 ± 1.24**

Mean horizontal gaze position during OKN at all stimulus velocities recorded using the infrared eye tracker. Values are normalised with respect to the direction of stimulus motion so that positive values indicate a ocular deviation in the direction opposite to curtain rotation. Average (mean ± standard error) of mean gaze position for all subjects (rightward and leftward curtain rotation combined) at each stimulus velocity also shown. Dir: curtain direction; R: rightward rotation; L: leftward rotation

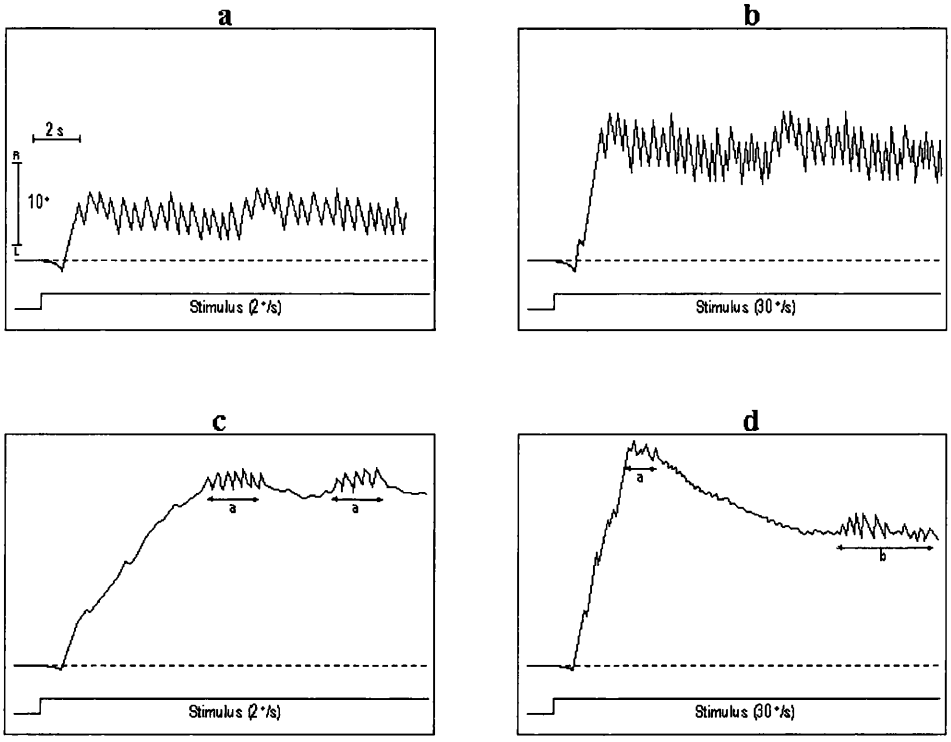
5.3.3. Results – Vestibulocerebellar patient

The vestibulocerebellar patient had a slow build-up of horizontal OKN. However, on optokinetic stimulation he immediately adopted an extreme contraversive deviation that was on average 26.4° (standard error = 1.4). This shift in gaze away from the primary position in the opposite direction to curtain rotation induced a gaze-evoked nystagmus with slow phases in the same direction as curtain rotation (Figure 5.4c and d).

The oculomotor examination revealed gaze-evoked nystagmus in horizontal and elevated gaze. Because the nystagmus was unaltered by monocular viewing, and reversed direction when either eye moved through the primary position, it was not manifest latent nystagmus. Rebound nystagmus was also noted. Horizontal smooth pursuit was completely saccadic. In the dark the decay of eye position indicated an integrator time constant of about 1-2s.

It was concluded that there was a complete smooth pursuit deficit and that the neural integrator had an abnormally short time constant. The smooth pursuit deficit also explained the slow build-up of horizontal OKN. Although these findings strongly suggest a cerebellar disorder, magnetic resonance imaging revealed no abnormality. Similar eye movement abnormalities (including extreme contraversion) were reported in ten other members of the family, with an autosomal pattern of inheritance (Harris *et al.*, 1993b).

Figure 5.4 Representative plots of OKN for a control subject and the child with a vestibularcerebellar disorder



The mean gaze position of OKN for a stimulus moving at 2°/s (a,c) and 30°/s (b,d) from right to left for subject AH (a,b) and the child with a vestibularcerebellar disorder (c,d). The dotted line indicates the primary gaze position. Arrows: (a) gaze-evoked nystagmus with slow phases in the same direction as curtain rotation (pseudo-OKN); (b) true OKN after slow build-up.

Table 5.4. Vestibulocerebellar patient - Mean horizontal gaze position during OKN

	STIMULUS VELOCITY (°/s)														
Dir	2	4	6	8	10	12	14	16	18	20	22	24	26	28	30
R	17.12	22.78	24.50	21.06	42.93	38.82	20.74	24.51	17.50	34.11	25.08	27.63	22.86	28.03	19.49
L	15.88	39.96	25.30	16.02	26.96	23.71	32.72	32.06	30.31	39.31	12.03	24.14	31.99	24.72	28.62

Mean horizontal gaze position during OKN at all stimulus velocities for the child with a vestibulocerebellar disorder. Values are normalised with respect to the direction of optokinetic curtain so that positive values indicate a ocular deviation in the direction opposite to curtain rotation. Dir: curtain direction R: rightward rotation; L: leftward rotation.

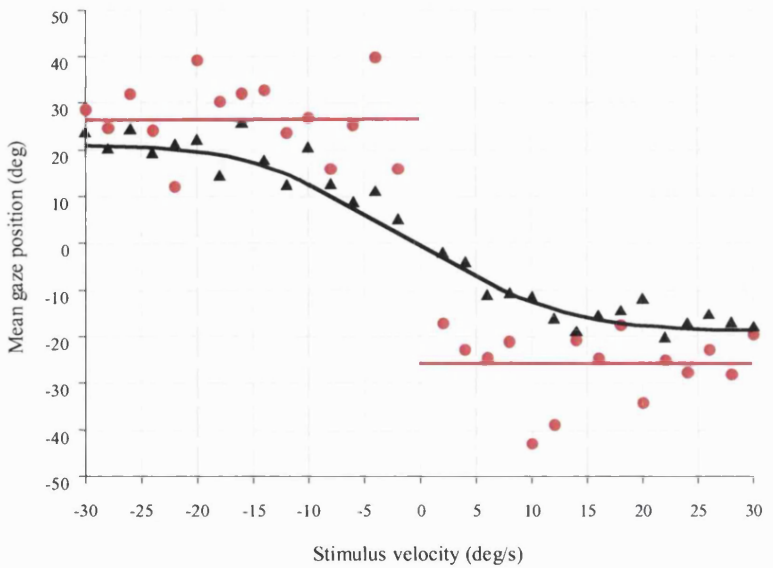


Figure 5.5 Mean gaze position - Vestibulocerebellar patient versus control subject

Mean gaze position plotted against stimulus velocity for the child with a vestibulocerebellar disorder and a representative response from a normal subject (LP). Negative values represent movements to the left.

5.4 Discussion

In this study we found that during OKN there was a shift of the mean gaze in the direction of the quick phase. This is consistent with a number of other studies that have examined gaze position during OKN in humans (Jung and Mittermaier, 1939; Miyoshi *et al.*, 1978; Dubois and Collewijn, 1979a; Abadi *et al.*, 1999; Thilo *et al.*, 2000; Watanabe, 2001). We also reported a decrease in OKN slow phase gain with increasing stimulation velocity, this too has been reported previously (Dichgans *et al.*, 1973; Hood, 1975; van Die and Collewijn, 1982; van den Berg and Collewijn, 1988; Holm-Jensen and Peitersen, 1997).

A number of experimenters have investigated the effects of central and peripheral retinal stimulation on gaze direction during OKN. The majority of them reported that gaze is always shifts in the direction of the quick phases during both central and peripheral retinal stimulation (Cheng and Outerbridge, 1975; Dubois and Collewijn, 1979a; Abadi *et al.*, 1999) but that a larger mean gaze shift occurs during central compared to peripheral retinal stimulation (Abadi *et al.*, 1999). In contrast, Hood (1967) reported that gaze was displaced in the direction of the slow phases during peripheral stimulation and Miyoshi *et al.* (1978) reported that gaze was displaced in the direction of the slow phases during central stimulation. These differences may be due to the instructions given to the subjects and whether look- or stare-OKN was elicited.

Hood and Leech (1974) investigated the effect of different perceptual strategies on horizontal OKN. During full-field optokinetic stimulation, when subjects were instructed to actively pursue the stimulus (look-OKN), mean horizontal gaze position deviated in the direction of the slow phases. In contrast, when subjects gazed

passively at the stripes (stare-OKN), nystagmus slow phases were reduced in velocity and the eyes were deviated in the direction of the quick phases. In this case it was the slow phases that returned the eyes towards primary gaze. Thus, in our experiment, all responses might be considered as characteristic of passive viewing (stare-OKN). The instructions that we gave to our subjects were intended to elicit stare-OKN.

Unlike previous reported studies on humans we looked at very slow stimulus speeds and found that even a stimulus moving at 2°/s brought about gaze shifts in the direction of the quick phase. For speeds between 2°/s and 10°/s there was a near linear relationship (r=0.99 for data recorded by IR) between stimulus speed and eccentricity of eye position, thereafter the response saturated. In the cat, Schweigart (1995) found that for stimulus velocities between 2°/s and 60°/s, gaze shifted in the direction of the quick phase and that gaze position depended on stimulus velocity. In contrast, Abadi *et al.* (1999) and Thilo *et al.* (2000) found that in humans the velocity of the stimulus had no significantly effect on the amplitude of the gaze shift. However, these investigators examined the response to stimulus motion above 20°/s (Abadi *et al.*, 1999) and 30°/s (Thilo *et al.*, 2000). Indeed, above 20°/s we also found that the amplitude of gaze shift was not dependent on stimulus velocity.

It has been suggested that in primates contraversion is under the control of the frontal eye fields (FEF) (Kubo *et al.*, 1981; Ouchi *et al.*, 1981; Fuchs and Mustari, 1993) and by the homologous structure in rats (dorsomedial shoulder of the prefrontal cortex) (Meier and Dieringer, 1993; Bähring *et al.*, 1994). Since the functional role of the FEF involves selective visual attention (Robinson and Fuchs, 1968; Ouchi *et al.*, 1981; Welch and Stuteville, 1985; Liechnetz and Goldberg, 1988), it has been suggested that contraversion may be interpreted as a shift of spatial attention (Meier and Dieringer, 1993; Bähring *et al.*, 1994; Watanabe, 2001). Watanabe (2001)

investigated this and demonstrated that during OKN manual reaction times were shorter when the target occurred in the direction from which stimulus motion originated (i.e. in the same direction as the shift of gaze position). This result was believed to be consistent with the idea that the subject's attention is moved along with the shift of gaze position. However, this shift of attention also occurred when a stationary fixation stimulus, that suppressed OKN, was present. Therefore, it appears that the purpose of the shift in gaze during OKN is not solely to shift attention since attention is shifted without a change in gaze position. Prompted by our observations from vestibulocerebellar patients we suggest an alternative explanation for the shift in gaze position.

The patient whom we studied was a member of a family with eye movement abnormalities. Ten members of this family were studied by Harris *et al.* (1993b). They found that the eye movement abnormalities seen in this family included poor or absent smooth pursuit and VOR suppression, gaze-paretic and rebound nystagmus, a short neural integrator time constant of 1-5s, slow build-up of horizontal OKN, mildly hyperactive VOR, and a high incidence of strabismus. This combination of oculomotor defects suggests an abnormality in the vestibulocerebellum. During horizontal OKN stimulation, varying degrees of contraversive deviation, some being quite extreme, were adopted by the affected patients studied by Harris *et al.* (Harris *et al.*, 1993b). Immediately on optokinetic stimulation the patient that we studied also adopted an extreme contraversive deviation. Therefore, we suggest that extreme contraversion during optokinetic testing might be another oculomotor sign of cerebellar dysfunction.

We found that in normal subjects contraversion is not an all-or-none phenomenon but that between 2°/s and 10°/s there was a near linear relationship

between stimulus velocity and gaze position. On the other hand, in the patient with very poor/absent smooth pursuit, no OKNe and a very leaky integrator, contraversion is a rapid all-or-none response. Only slow build-up OKN was observed although the contraversion was immediate and thus, the stimulus for contraversion cannot be slow phase eye velocity but may be an internal reconstruction of stimulus velocity (e.g. efference copy) or retinal slip. The patient also had gaze-evoked nystagmus, which results from poor gaze holding ability due to neural integrator dysfunction. In neural integrator dysfunction the integrator does not maintain sufficient tonic innervation to the extraocular muscles for the eyes to remain at an eccentric orbital position, and they are pulled back to the primary position by the elastic forces of the orbital fascia. Repeated corrective quick phases are then needed to move the eyes back towards the desired position in the orbit. Contraversion induced such a gaze-evoked nystagmus in the patient and this nystagmus had slow phases that were in the same direction as stimulus motion. Therefore, we suggest that the extreme contraversion seen in vestibulocerebellar patients reflects a 'vestigial' system which attempts to match the gaze-evoked nystagmus slow phases with stimulus velocity. As velocity matching would be enhanced by even a slightly imperfect integrator, a similar strategy to enhance velocity-matching could explain the less dramatic and graded contraversion in normal subjects. Presumably, in normal subjects the response saturates above 10°/s since the enhancement required to precisely match stimulus velocity is beyond that that could be achieved with any gaze-evoked nystagmus resulting from a slightly imperfect integrator. However, before this theory can be considered any further studies are required to relate measures of neural integrator time constants to the amount of contraversion in normal subjects and in patients with cerebellar disorders.

5.5 Conclusion

In this chapter we examined gaze position during full-field horizontal OKN. We found that the quick phases of OKN move the eyes in the direction opposite to stimulus movement ("contraversion"). This is a robust phenomenon, occurring in all subjects over a range of stimulus speeds (2-30°/s). We had previously observed excessive contraversion in the clinical setting and in this experiment we confirmed this clinical observation by documenting a case of extreme contraversion in a patients with a vestibulocerebellar disorder.

So far the only explanation proposed for this shift in gaze position during horizontal OKN is that it enables perusal of the oncoming visual scene. We propose another explanation for this behaviour based on the idea that a leaky neural integrator could be used to enhance velocity-matching. Further, we suggest that it is important to recognise a large (>20°) contraversive deviation in the clinical setting, as it may be a sign of cerebellar disease.

Chapter 6 - Normal Vertical Optokinetic Nystagmus and Vertical Saccades

6.1 Introduction

The recording and analysis of horizontal eye movements has been shown to be a useful method of diagnosing and characterising various ocular motility disorders. On the other hand, there has been relatively little study of vertical eye movements, probably because they are difficult to stimulate, evaluate and record precisely. Since the anatomical pathways controlling horizontal and vertical eye movements are different, at least in some respects, lesions and disease processes may affect one meridian or the other or both. Therefore to the clinician it may be just as useful to test vertical eye movements as it is to test horizontal ones.

In this chapter we investigate the characteristics of vertical OKN and vertical saccades in normal adult subjects. We look at both the slow and quick phases of vertical OKN and compare the temporal characteristics – that is, the amplitude, duration and peak velocity of vertical quick phases and vertical saccades.

6.1.1 Normal vertical saccades

An extensive number of experiments have been conducted with the aim of characterising the quantitative and qualitative properties of horizontal saccadic eye movements. On the other hand, vertical saccades have rarely been investigated systematically, mainly because it is difficult to measure them reliably. The vertical electro-oculogram is heavily contaminated by lid movement artefacts (Barry and

Melvill-Jones, 1965; Ford, 1976) and overestimates the velocities of up saccades (Yee *et al.*, 1985). Infrared limbus tracking methods also show serious distortions in the vertical direction and underestimate the velocities of up saccades (Yee *et al.*, 1985). Although the magnetic search coil technique allows for accurate recording of vertical eye movements without distortion by concomitant lid movements it has the disadvantages of being expensive, causing slight irritation of the eye and requiring more co-operation of the subject (Yee *et al.*, 1985). However saccades up to 20° in the upper field of the orbit and up to 30° in the lower field may be recorded without obvious artefacts in their trajectories or errors in calculations of their peak velocities (Yee *et al.*, 1985). With the more widespread use of the magnetic search coil technique, significant observations concerning vertical saccades have been made in human subjects. Only studies that recorded saccades using the magnetic search coil will be discussed in the following sections (6.1.1.1 and 6.1.1.2).

6.1.1.1 Differences between upward and downward saccades

Yee *et al.* (1985) elicited voluntary vertical saccades of amplitudes between 5° and 35° and found that up and down saccades to and from the centre had similar peak velocities in normal human subjects. However, a difference of up to 20% was present in individual subjects. Chioran and Yee (1991) also found that for amplitudes between 5° and 35° there was no difference in the peak velocities of upward and downward saccades. Similarly, Collewijn *et al.* (1988b) reported that upward and downward saccades up to 30° were very alike in peak velocity and duration, as well as in velocity profiles. The characteristics of upward saccades, however, depended heavily on the part of the visual field in which the saccades were made. In the upper field upward (centrifugal) saccades had lower peak velocities and longer durations

compared to similar (centripetal) saccades in the lower visual field. Downward saccades were almost independent of eye position.

Huaman and Sharpe (1993) studied three groups of normal subjects: thirteen young subjects (mean age 28.3 ± 4.6 years); ten middle-aged subjects (mean age 49.8 ± 9 years) and sixteen elderly subjects (mean age 71.9 ± 5.5 years). They found no significant difference in the peak velocities of upward and downward saccades up to 30° within each age group, although individual young subjects made significantly faster upward than downward saccades.

Becker and Jürgens (1990) compared the peak velocities of saccades evoked by target steps of 20°. They found that over all subjects downward saccades were slower than saccades in the upward direction by about 12%. However, these differences were statistically insignificant.

Small systematic differences in amplitude between upward and downward saccades have been noted. Collewijn *et al.* (1988b) found that for target distances between 10 and 70°, upward saccades undershoot the target by about 10%. Downward saccades, in contrast to upward and horizontal saccades, tended to overshoot the target for target distances up to 40° but there was a slight undershoot for larger amplitudes.

6.1.1.2 Differences between vertical and horizontal saccades

In seven normal human subjects, Leigh *et al.* (1982) analysed the peak velocity-amplitude relationships of 609 vertical and 274 horizontal saccades of amplitudes up to 30°. The horizontal and vertical saccades had similar peak velocities, although the vertical saccades showed a greater scatter. Other investigators did not agree and noted differences between horizontal and vertical saccades. Collewijn *et al.* (1988b) found that the peak velocities of vertical saccades up to 40° were lower than

those of horizontal saccades. However for amplitudes larger than 50° the reverse was true. This was because the peak velocities of vertical saccades began to saturate only at the larger amplitudes (amplitudes up to 70° were elicited), in contrast with horizontal saccades where the saturation was more pronounced (Collewijn *et al.*, 1988a).

Becker and Jürgens (1990) found that, on average, downward saccades were slower than those in the three other cardinal directions but saccades in the upward direction reached almost the same velocity and duration as horizontal saccades. However, it should be kept in mind that the values given by Becker and Jürgens were for a specific amplitude (20°). The work of Collewijn *et al.* (1988b) suggests that the main sequence for peak velocity of horizontal and vertical saccades may have different shapes. Hence, differences between horizontal and vertical velocities might depend on the amplitude under consideration.

6.1.2 Normal vertical optokinetic nystagmus

Vertical OKN is asymmetrical in many species and these asymmetries are present under both monocular and binocular conditions. In monkeys, cats and chickens upward stimulus movement elicits a better response than downward movement (monkey (Cohen *et al.*, 1977; Takahashi and Igarashi, 1977; Igarashi *et al.*, 1978; Matsuo and Cohen, 1984; Himi *et al.*, 1988; Himi *et al.*, 1990); cat (Collins *et al.*, 1970; Vital-Durand and Jeannerod, 1974; Evinger and Fuchs, 1978; Darlot *et al.*, 1981; King and Leigh, 1982); chicken (Wallman and Velez, 1985)). In the monkey it has been shown that this upward preponderance is greater at higher velocities (Matsuo and Cohen, 1984; Grasse and Cynader, 1988) and extends to vertical OKAN as well, velocity storage being comparatively weak for OKN with slow phases directed

downward (Matsuo *et al.*, 1979; Matsuo and Cohen, 1984; Himi *et al.*, 1988; Himi *et al.*, 1990). In the rabbit a preference for downward stimulus movement was reported by Erickson and Barmack (1980) whereas, Collewijn and Noorduin (1972) found that nearly symmetrical OKN was measured in response to both downward and upward stimulus movement.

Investigations of differences in the vertical OKN in normal humans produced inconsistent results. Some investigators reported a preference for upward stimulus movement and some for downward stimulus movement while others found idiosyncratic differences in the directional asymmetry without a significant group effect (see Table 6.1). The results of these investigations are difficult to interpret, however, because of methodological concerns. It is not clear whether the discrepancies in the conclusions reached result from individual differences among normal adults, or from the method used to record vertical OKN, or from the stimuli used to elicit it.

Many investigators used electro-oculography (EOG) to measure eye movements (Collins *et al.*, 1970; Takahashi *et al.*, 1978; Baloh *et al.*, 1983; Calhoun *et al.*, 1983; Thomas and Saunders, 1984; Abadi and Dickinson, 1985; Clément *et al.*, 1986; Leliever and Correia, 1987; Wei *et al.*, 1992). As mentioned in 6.1.1 in this technique the recordings are highly contaminated by the changes in eyelid position that accompanies vertical OKN and greater upward vertical OKN gains might result.

Earlier reports of a lack of vertical asymmetry in human OKN were based on quick phase frequency, not slow phase velocity (Stiefel and Smith, 1962; Smith, 1962). Again, because of the influence of the lids, this is a particularly unreliable measure of vertical OKN (Guedry and Benson, 1971).

Some investigators used an infrared limbal reflection technique to record vertical OKN (Schor and Levi, 1980; Tsuzuku *et al.*, 1995; Shallo-Hoffmann *et al.*, 1999), however with vertical recordings the eyelid margins can obscure the limbus superiorly and inferiorly.

Two studies were conducted with the subject's head tilted (Collins *et al.*, 1970; Baloh *et al.*, 1983), however, subsequent experiments found that the gains of vertical OKN and OKAN are affected by head position (Calhoun *et al.*, 1983; Matsuo and Cohen, 1984; Leliever and Correia, 1987).

A further issue is the stimulus velocity used to elicit vertical OKN. Hainline *et al.* (1984a) and Schor and Levi (1980) used a very slow stimulus velocity (7 and 6°/s respectively). In these studies the response was probably dominated by the smooth pursuit system. Other investigators have employed a stimulus velocity of 20°/s (Calhoun *et al.*, 1983; Clément *et al.*, 1986) or 24°/s (Collins *et al.*, 1970) and some have used 40°/s or above (Takahashi *et al.*, 1978; Clément *et al.*, 1986; Leliever and Correia, 1987; van den Berg and Collewijn, 1988; Murasugi and Howard, 1989). The groups who used a stimulus velocity of 20 or 24°/s did not report an asymmetry between up and down responses, whereas the groups who used a stimulus with a velocity of 40°/s or above found a significant asymmetry.

Four studies have measured vertical OKN in normal upright subjects using the magnetic search coil method. Van den Berg and Collewijn (1988) reported a consistent upward preponderance in human OKN – that is, the gains of OKN in response to upward stimulus movement are higher than those in response to downward stimulus movement. These investigators used a large random dot display and found this directional asymmetry at stimulus velocities between 9 and 57°/s in six of seven normal subjects. Murasugi and Howard (1989), using similar methods, found

that between 30 and 70°/s, seven of ten subjects generate higher OKN gains in response to upward than to downward stimulus motion. Ogino and co-workers (1996) reported the same asymmetry between up and down OKN in twenty subjects viewing a striped stimulus covering the entire visual field. In this study statistical significance was noted for stimulus velocities of 30-60°/s, but not for higher velocities, because vertical OKN saturated at around 40-50°/s. On the other hand, Böhmer and Baloh (1991), found no consistent up-down OKN asymmetry for six subjects viewing a 90 x 90° striped stimulus moving at 15-60°/s.

Thus the question of whether vertical OKN in normal adult subjects is symmetrical or asymmetrical is still not absolutely clear. In this experiment we re-examined this issue and compared the slow phase velocity gain of upward OKN with downward OKN recorded from upright subjects in response to a large field display over a range of stimulus speeds and spatial frequencies. Eye movements were recorded using the magnetic search coil technique.

Table 6.1 Details of previous studies of vertical OKN in human subjects.

	Year	Recording Method	Stimulus	Stimulus speed/ Instructions	Subjects	Measure	Conclusions
Shallo-Hoffmann et al.	1999	IR	0.23 cycles/° sinusoidal grating, 43cm diameter, subtending 18.3°	1,3,6°/s for 60s "Look at the stripes"	10 23-52 yrs	Binoc SPV	Up=down Gain=1
Correia et al.	1997	EOG ISCAN	Hemisphere covering 180° of visual field at 1m Stripes 10° width	40 and 60°/s 45s stimulation 30s darkness "Stare through the stripes"	9 28 ± 2 yrs	SPV each nystagmus beat (straight line slope)	6/9 subjects up>down
Ogino et al.	1996	MSSC	Hemispheric screen, 80cm diameter Stripes 4° white, 24° black	30,40,50,60,70,80, 90°/s. 15s stimulation. "Follow the stripes"	20 22-28 yrs	Mean SPV for first 5s	Up>down, statistically significant for stimulus velocities 30-60°/s ($p<0.01$). Vertical OKN saturated around 40-50°/s
Tsuzuku et al.	1995	IR	Random dots Temp freq=5.55Hz	40°/s "Look at passing dots, allow eyes to move freely"	5 35-58 yrs	Binoc SPV Frequency Amplitude	Up>Down not statistically significant at 1% Statistically significant at 5%
Wei et al.	1994	EOG	Hemisphere 100cm diameter Stripes 2° white 18° black	40°/s 60s stimulation 60s dark "Try to follow each stripe"	18 20-35 yrs	Binoc SPV of last 5s of each trial	Up>down ($p<0.05$) Asymmetry increased in 90° roll
Wei et al.	1992	EOG	Hemisphere 100cm diameter Stripes 2° white 18° black	20,40,60,80°/s 60s stimulation 60s dark "Try to follow each stripe"	11 22-35 yrs	SPV of last 5s of each trial	Up=down at 20°/s Up>down at 40,60°/s (not statistically significant) Down>up at 80°/s 40°/s best stimulus
Böhmer and Baloh	1991	MSSC	Screen 90 x 90cm Stripes 3°	15,30,45,60°/s "Look at stripes directly in front"	6	Binoc SPV average for 30s	Up=down Up OKAN>down OKAN. No effect of static head position (upright v lateral)
Murasugi and Howard	1989	MSSC	Screen 61 x 64° Random dots	10,30,50,70°/s "Viewing relaxed but attentive. Do not follow individual feature"	10 24-60 yrs	Mean SPV of 15s trial	7/10 subjects up>down gain ca. 0.15 larger
van den Berg and Collewijn	1988	MSSC	Hemispherical radius:80cm Random dots	9,23,36,56°/s "Stare OKN"	7	Binoc & monoc SPV for 8s	6/7 subjects up>down gain ca. 0.15 larger 1/7 subjects up=down
Leliever and Correia	1987	EOG	Hemisphere covering 180° of visual field	40,50,60,70°/s 45s stimulation 45s dark "Actively pursue stripes"	21	Binoc SPV from 3 nystagmus beats	Up>down at 40,50,60°/s No asymmetry at 70°/s Amplitudes of up slow phases greater
Clément et al.	1986	EOG	Checkerboard pattern Square=5°	20, 53°/s 40s stimulation 20s dark	3	Binoc SPV between 20 and 40s after stimulus onset	Up>down

Abadi and Dickinson	1985	EOG	Semicylindrical 130° of vertical, 42° horizontal visual field Stripes 7°black 4°white	10,30,50,80°/s Each 30 sec duration "Stare OKN"	9 20-50 yrs	Binoc SPV	8/9 subjects up=down or up>down 1/9 subjects down>up
Hainline et al.	1984a	IR	Screen 30° by 22° At 78cm Spatial frequency = 0.3cycles/°	7°/s 20s stimulation 5s inter-trial interval "Stare at centre of screen, keep moving bars visible"	7 18-36 yrs	Binoc SPV (linear regression line) Amplitude Duration	Up=down
Thomson and Saunders	1984	EOG	Spots of light, pseudo-random size screen subtending 45° at 2m	10,20,30,40,50,60,70,80,90, 100°/s each 30s "Stare, don't follow targets"	10 young adults	Binoc beat freq	Up=down below 20°/s, Down>up above 20°/s
Baloh et al.	1983	EOG	Head tilted 90° OKN drum 1m in diameter Black interior, 2.5cm white stripes at 15.6° intervals	Sinusoidal rotation – 0.05Hz, peak velocity 60°/s. Step stimulus - 60°/s 60s stimulation	10	Binoc SPV	Down>up but not statistically significant
Calhound et al.	1983	EOG	Stripes 5°black 1°white Screen subtending 92° at 70cm	20°/s for 45 s, 60s darkness	17 23-56 yrs	Binoc SPV	No consistent asymmetry Up>down 7/17 subjects Down>up 9/17 subjects; Up=down 1/17 subjects Lateral tilt no effect on vertical OKN
Schor and Levi	1980	Photoelectic IR	Sinusoidal grating 1cycle/° Screen subtending 8 by 10° at 71cm	6°/s Stare at centre, keep moving stripes visible	5	SPV of 20s recording	Up=down 3/5 Down>up (10% reduction) 2/5
Takahashi et al.	1978	EOG	Stripes "Pursue the striped pattern as rapidly as possible"	10-200°/s in 10°/s steps	20	Binoc SPV	Up>down above 70°/s Up more variable
Collins et al.	1970	EOG	Head tilted 90° OKN drum 1.2m diameter, 75cm high White interior, 2.5cm black stripes at 5cm	24°/s for 30s 120s darkness	10 21-37 yrs	Binoc SPV and beat freq	Up=down
Stiefel and Smith	1962	EOG	Hand-held OKN drum 2.5cm black stripes on white background	1.5 stripes/s	20 20-73 yrs	Beat freq in 12s	Up=down, occasionally down>up

EOG = DC electro-oculography; IR = infrared reflection technique; MSSC = magnetic scleral search coil; ISCAN = Infrared video-based system; temp freq = temporal frequency of stimulus; yrs = years (age); binoc = both eyes viewing; monoc = one eye viewing; SPV = slow phase velocity

6.2 Methodology

6.2.1 Subjects and recording methods

Eight healthy adult subjects were recorded (four male, four female). Their ages ranged between 24 and 54 years. None had any known neurological or visual defects other than refractive anomalies. Informed consent was obtained from the subjects after the nature of the procedures had been explained fully.

Horizontal and vertical movements were recorded using the magnetic search-coil technique. Four subjects wore a search coil in each eye and four wore only one search coil. A neck rest supported subjects' heads and the importance of keeping their heads still was stressed. Alertness was maintained by frequent verbal encouragement. Subjects were randomly assigned as to whether they had vertical OKN or vertical saccades tested first.

6.2.2 Visual stimuli

The OKN stimulus was rear-projected onto a semi-translucent tangent screen at a viewing distance of 1 m (See Chapter 2 - Figure 2.2). The stimulus subtended 72° horizontally and 60° vertically and consisted of alternating horizontal black-and-white stripes, with luminance of 0.7 and 13.7 cd/m^2, respectively. Stripes were chosen in preference to a random dot display because it has previously been shown that larger quick phase amplitudes are elicited with a striped pattern (Watanabe *et al.*, 1994). The stimulus moved upward or downward using one of three spatial frequencies: 0.04, 0.08 and 0.16 cycles/°. The direction and spatial frequency of the stimulus were randomised. Each sequence was viewed with both eyes open and the stimulus moved

at 10, 20, 30, 40 and 50°/s for periods of 20s each. The screen was blanked for 10s between each sequence. Subjects were instructed to keep gazing into the centre of the pattern, being careful to maintain optimal clarity of the stripes but not to deliberately follow any of the stripes.

The stimulus for eliciting vertical saccades consisted of 23 black dots displayed on the screen. One dot was displayed in the centre, one 1° above and below the centre and thereafter one every 2° above and below up to 20° eccentricity. To elicit voluntary vertical saccades subjects were instructed to perform two patterns of refixations. In the walk-up pattern they were asked to refixate from the centre dot to the dot located at 1° in the upper field, back to the centre dot, to the 2° dot, back to the centre dot, and to successive eccentric dots until the 20° dot had been reached. In this pattern up and down saccades were made entirely within the upper visual field. In the walk-down pattern refixations were made between the centre dot and the dots in the lower field. In this pattern up and down saccades were made within the lower field.

Horizontal saccades were also elicited. The stimulus was the same as that for vertical saccades, rotated through 90°.

6.2.3 Data analysis

Our standard computer program was used to determine the characteristics of the eye movements (Chapter 2). A saccade or OKN quick phase (FEM) was detected when the velocity was continuously above 10°/s for at least five points. Preliminary experiments demonstrated that the majority of quick phases elicited during vertical OKN were <10°. Therefore this lower threshold (compared to that used to detect horizontal FEMs, see Chapter 3) was chosen to ensure that these small FEMs were detected. All measurements were checked interactively and eye movements associated

with blinks were rejected. We separately analysed data from each eye in the four subjects who wore a coil in both eyes.

6.3 Results

6.3.1 Comparison of upward with downward eye movements

Saccades up to 20° in amplitude were elicited in this experiment. Above 4° the relationship between duration and amplitude is linear, therefore, to compare the durations of saccades we took the slope and intercept values of a linear regression over a 4-20° range. Like those in the horizontal plane the relationship between peak velocity and amplitude of vertical saccades is not linear. Therefore logarithmic (base 10) plots of peak velocity against amplitude (for amplitudes >4°) were constructed before performing a linear regression.

6.3.1.1 Centrifugal versus centripetal vertical saccades

Initially we examined saccades made in the upper visual field separately from those made in the lower field. There were no differences in the duration (MANOVA, $p=0.43$, Hotellings T-test) or peak velocity ($p=0.74$) of upward saccades made in the upper (centrifugal saccades) and lower (centripetal saccades) visual field. Similarly, there were no differences in the duration ($p=0.71$) or peak velocity ($p=0.74$) of downward saccades made in the upper (centripetal saccades) and lower (centrifugal saccades) visual field. Thus we found that upward and downward saccades were independent of eye position and, therefore, for the remainder of the analysis we considered centripetal and centrifugal saccades together.

6.3.1.2 Upward versus downward fast eye movements

Table 6.2 gives the main sequence parameters for all vertical saccades of 4 - 20° in amplitude. For the group as a whole there was no significant difference in the duration (p=0.69) or peak velocity (p=0.27) between upward and downward saccades.

Similarly, for the group as a whole there was no significant difference in the duration (p=0.66) or peak velocity (p=0.68) between upward and downward OKN quick phases (see Table 6.4).

Table 6.2. Main sequence parameters for vertical saccades

		Main Sequence for Duration				Main Sequence for Peak Velocity			
		Up		Down		Up		Down	
		S	I	S	I	S	I	S	I
		ms/°	ms	ms/°	ms				
RL	RE	4.47	28.72	6.02	35.23	0.53	1.86	0.42	1.93
	LE	4.19	34.04	5.81	33.53	0.45	1.91	0.44	1.92
AK	RE	5.79	15.16	6.62	28.75	0.33	2.06	0.32	1.95
	LE	5.85	15.33	7.07	25.42	0.32	2.07	0.29	1.97
HH	RE	3.62	31.13	3.76	32.66	0.52	1.86	0.43	1.97
	LE	2.68	34.28	4.29	27.35	0.57	1.83	0.44	1.95
SG	RE	7.03	43.28	7.61	39.23	0.57	1.69	0.38	1.87
	LE	6.58	42.22	5.30	43.26	0.69	1.61	0.41	1.89
JS	RE	3.69	34.09	2.21	38.61	0.45	1.88	0.66	1.78
RR	RE	3.31	35.63	3.31	29.14	0.59	1.88	0.45	1.90
ST	LE	4.81	17.80	4.60	27.84	0.35	2.06	0.39	1.96
JL	LE	3.52	29.12	2.96	27.84	0.52	1.87	0.45	2.02
MEAN		**4.63**	**30.07**	**4.96**	**32.41**	**0.49**	**1.88**	**0.42**	**1.93**
±		±	±	±	±	±	±	±	±
SE		**0.40**	**2.75**	**0.50**	**1.63**	**0.03**	**0.04**	**0.03**	**0.02**

The slope (S) and intercept (I) for the duration-amplitude relation were obtained from a linear regression of the main sequence for duration for amplitudes >4°.
The slope (S) and intercept (I) values for the peak velocity-amplitude relation were obtained from a linear regression of the logged main sequence for peak velocity for amplitudes >4°. Pooled means (±standard error) also shown.

6.3.2 Comparison of vertical saccades with horizontal saccades

We also compared vertical saccades with horizontal (centripetal and centrifugal combined) saccades and found that they had a significantly different duration and peak velocity ($p<0.001$). Vertical saccades were far slower than horizontal saccades, with longer durations and lower peak velocities (Figure 6.1, Tables 6.2 and 6.3).

Table 6.3. Main sequence parameters for horizontal saccades

		Main Sequence for Duration				Main Sequence for Peak Velocity			
		Right		Left		Right		Left	
		S	I	S	I	S	I	S	I
		ms/°	ms	ms/°	ms				
RL	RE	3.15	19.45	3.20	19.18	0.34	2.16	0.35	2.15
	LE	3.10	20.56	3.13	20.59	0.30	2.14	0.31	2.14
AK	RE	3.41	24.11	3.39	21.88	0.42	1.99	0.42	2.01
	LE	3.42	25.27	3.53	21.19	0.45	1.95	0.41	2.01
HH	RE	2.96	24.83	2.95	23.64	0.44	2.04	0.43	2.05
	LE	2.86	25.37	2.85	24.19	0.44	2.04	0.44	2.04
SG	RE	1.70	29.52	1.77	28.87	0.54	2.01	0.55	1.99
	LE	1.74	30.71	1.69	28.07	0.60	1.93	0.54	2.00
JS	RE	2.82	29.80	2.72	32.58	0.46	1.96	0.51	1.91
RR	RE	2.82	25.73	2.68	26.04	0.43	2.06	0.46	2.03
ST	LE	3.52	21.47	3.60	20.88	0.36	2.05	0.37	2.04
JL	LE	2.79	27.67	2.66	23.16	0.41	2.04	0.39	2.10
MEAN		**2.86**	**25.37**	**2.85**	**24.19**	**0.43**	**2.03**	**0.43**	**2.04**
±		±	±	±	±	±	±	±	±
SE		**0.17**	**1.05**	**0.18**	**1.15**	**0.02**	**0.02**	**0.02**	**0.02**

The slope (S) and intercept (I) for the duration-amplitude relation were obtained from a linear regression of the main sequence for duration for amplitudes >4°.
The slope (S) and intercept (I) values for the peak velocity-amplitude relation were obtained from a linear regression of the logged main sequence for peak velocity for amplitudes >4°. Pooled means (±standard error) also shown.

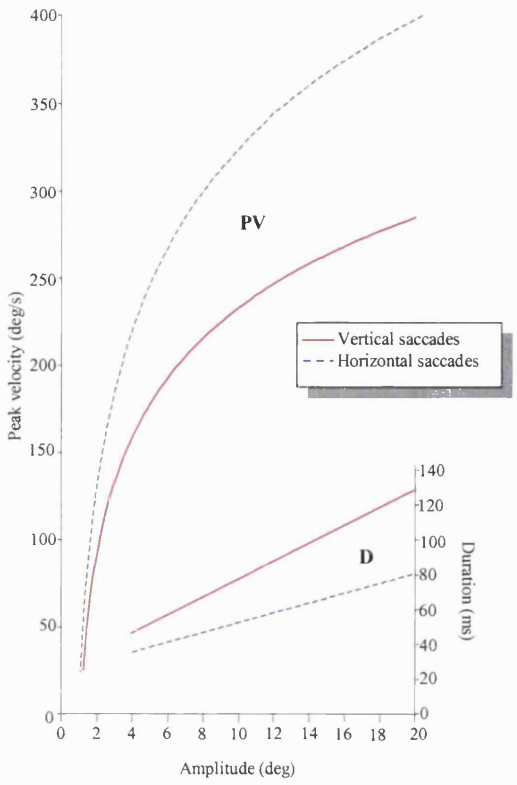


Figure 6.1. The main sequences for horizontal and vertical saccades

The main sequence for duration (D) and for peak velocity (PV) of horizontal and vertical saccades. These plots were derived from all the saccades recorded in this experiment. Linear regressions were fitted to the main sequences for duration (for amplitudes >4°). Logarithmic regressions were fitted to the main sequences for peak velocity.

6.3.3 Comparison of vertical saccades with vertical OKN quick phases

In Chapter 3 we compared the main sequence for duration of horizontal saccades with the main sequence for duration of horizontal OKN quick phases by calculating the slope and intercept of a linear regression over a 4-25° range. In this chapter we found that the quick phases of *vertical* OKN were much smaller that horizontal quick phases and very few vertical quick phases had an amplitude greater than 10° (average=3.05, see Figure 6.2). Therefore, in this experiment we compared only saccades and quick phases that were <10° in amplitude. The relationship between saccadic duration and amplitude and saccadic peak velocity and amplitude over this range is *not* a linear one (Figure 6.3a and 6.3c) and therefore logarithmic

(base 10) plots of the main sequences for duration *and* peak velocity (Figure 6.3b and 6.3d) were constructed for each subject before performing linear regressions.

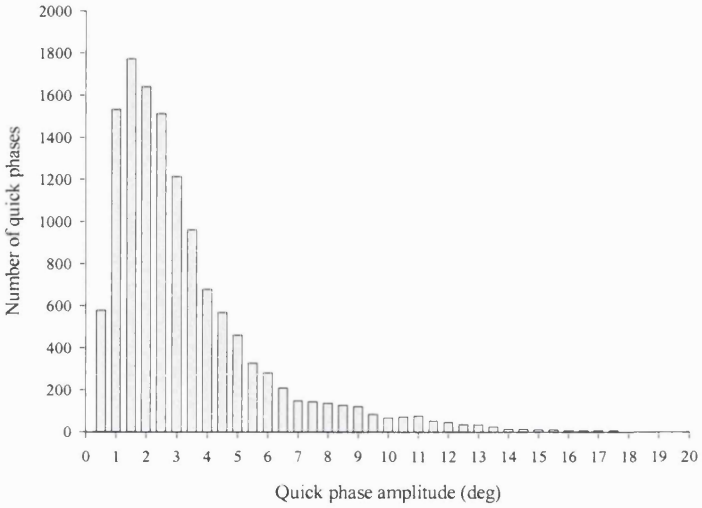
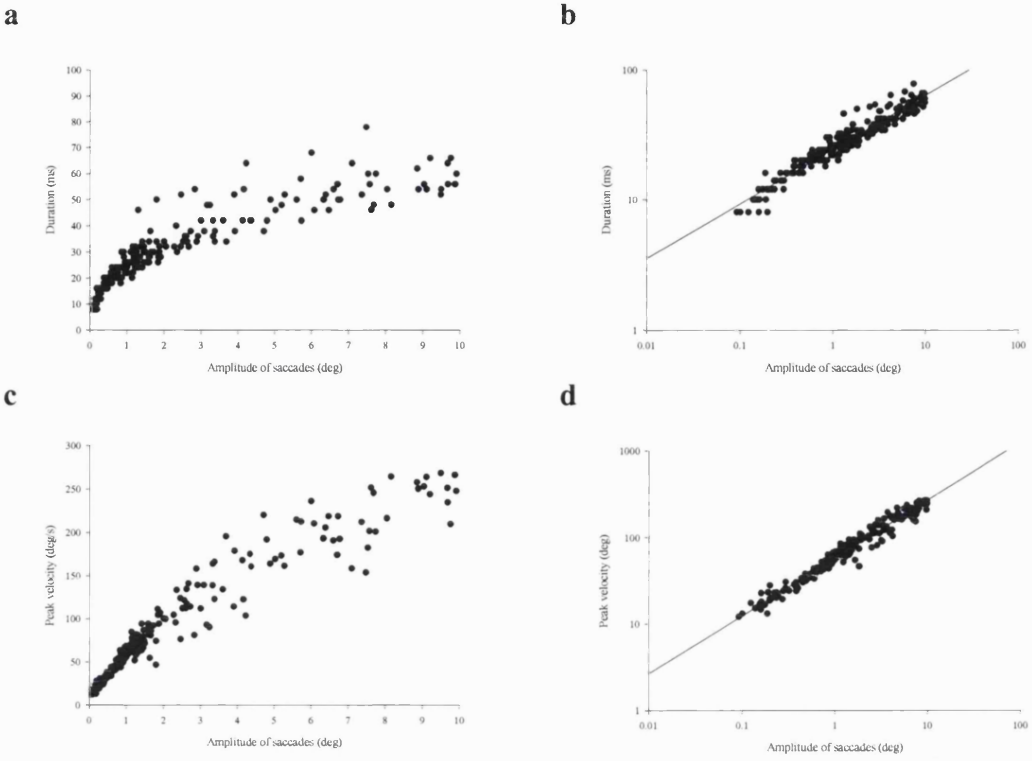


Figure 6.2. Vertical OKN quick phase amplitudes

Histogram to show the amplitudes of all vertical OKN quick phases elicited from 12 eyes of 8 subjects.

Figure 6.3. Typical vertical saccadic main sequences for duration and peak velocity



These plots were derived from vertical saccades <10° amplitude (upward and downward combined) recorded from subject HH. (a) Plot demonstrating non-linear relation between duration and saccadic amplitude below 10°. (b) Logarithmic plot of duration versus amplitude. Linear regression line also shown. (c) Plot demonstrating non-linear relation between peak velocity and amplitude below 10°. (d) Logarithmic plot of peak velocity versus amplitude. Linear regression line also shown.

6.3.3.1 The main sequence for duration

Each subject's main sequence for duration for vertical saccades and vertical OKN quick phases (<10° amplitude) is illustrated in Figure 6.4. It can be seen that although the main sequences for duration of these two FEMs are similar they are not identical; vertical OKN quick phases showed a greater scatter and tended to have a longer duration. Statistical testing (MANOVA) demonstrated that the differences in the durations of vertical saccades and OKN quick phases *were* just significant (p=0.01 for upward FEMs, p=0.04 for downward FEMs, Hotellings T-test).

Figure 6.4. Saccadic and OKN quick phase main sequences for duration

Scatter plots of the vertical saccadic and vertical OKN quick phase main sequences for duration for each subject. Negative values represent eye movements downward. Continued overleaf.

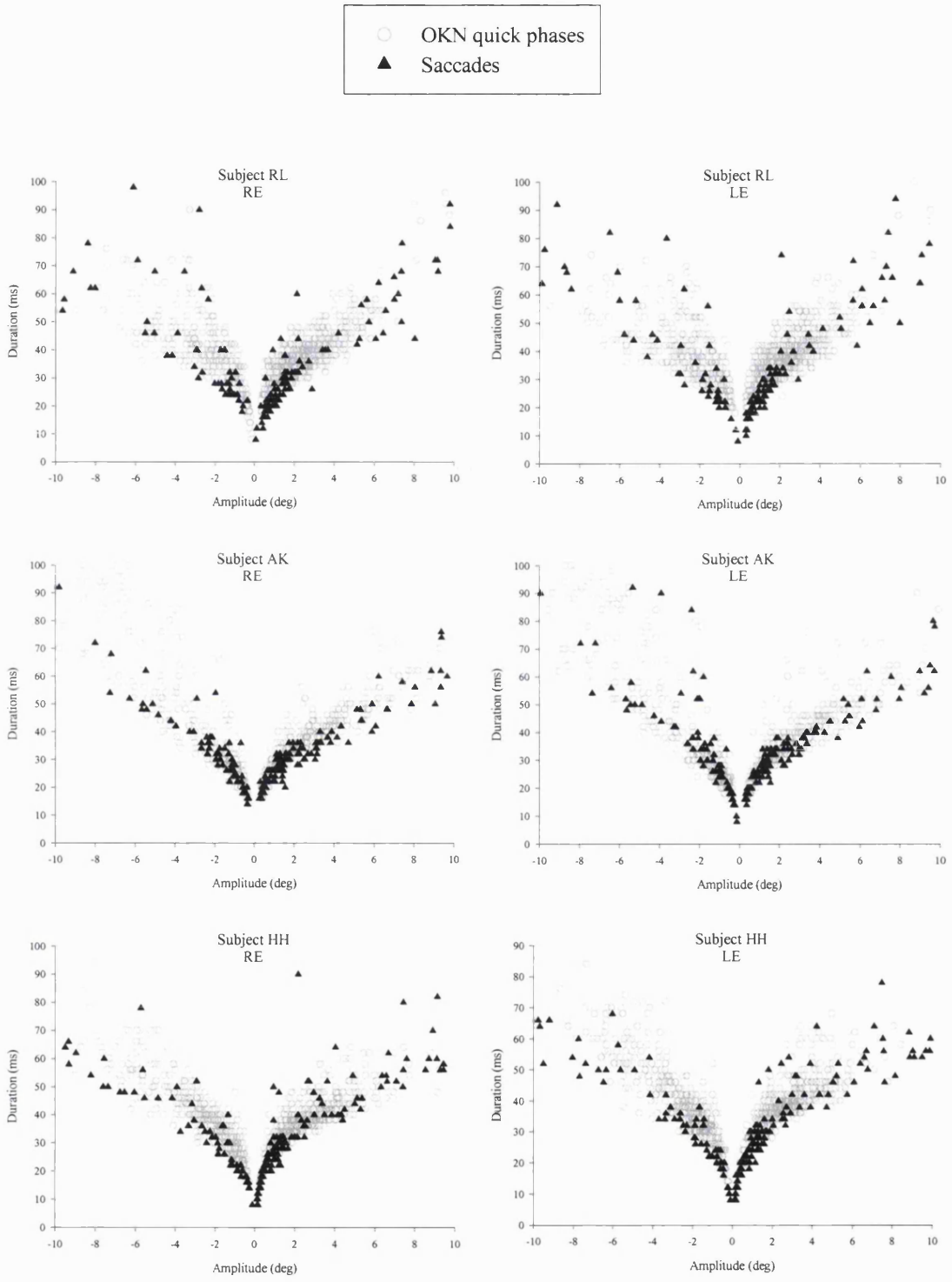
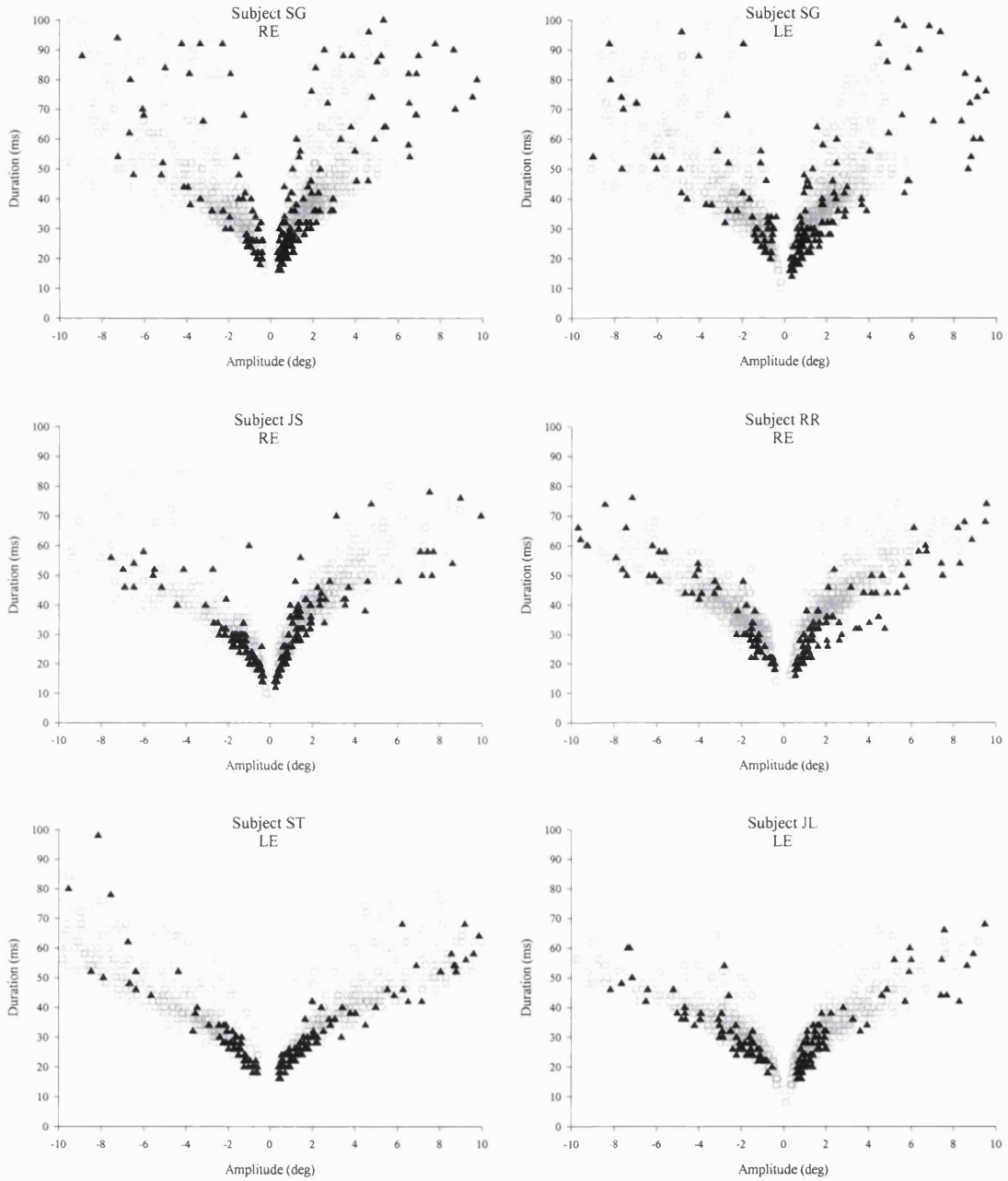


Figure 6.4. Continued



6.3.3.2 The main sequence for peak velocity

Each subject's main sequence for peak velocity for vertical saccades and vertical OKN quick phases (<10° amplitude) is illustrated in Figure 6.5. Again the main sequences of these two FEMs are similar but not identical; vertical OKN quick phases showed a greater scatter and tended to have a lower peak velocity. The differences in the peak velocities of vertical saccades and OKN quick phases were also statistically significant ($p<0.01$ for upward FEMs, $p=0.04$ for downward FEMs, Hotellings T-test).

Figure 6.5. Saccadic and OKN quick phase main sequences for peak velocity

Scatter plots of the vertical saccadic and vertical OKN quick phase main sequences for peak velocity for each subject. Negative values represent eye movements downward. Continued overleaf.

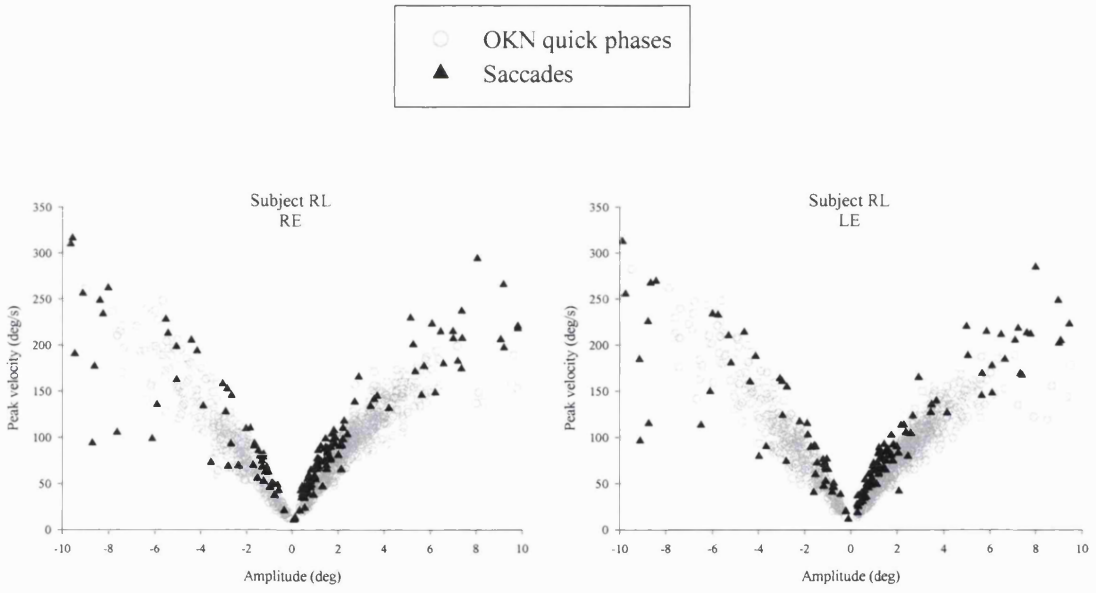


Figure 6.5. Continued

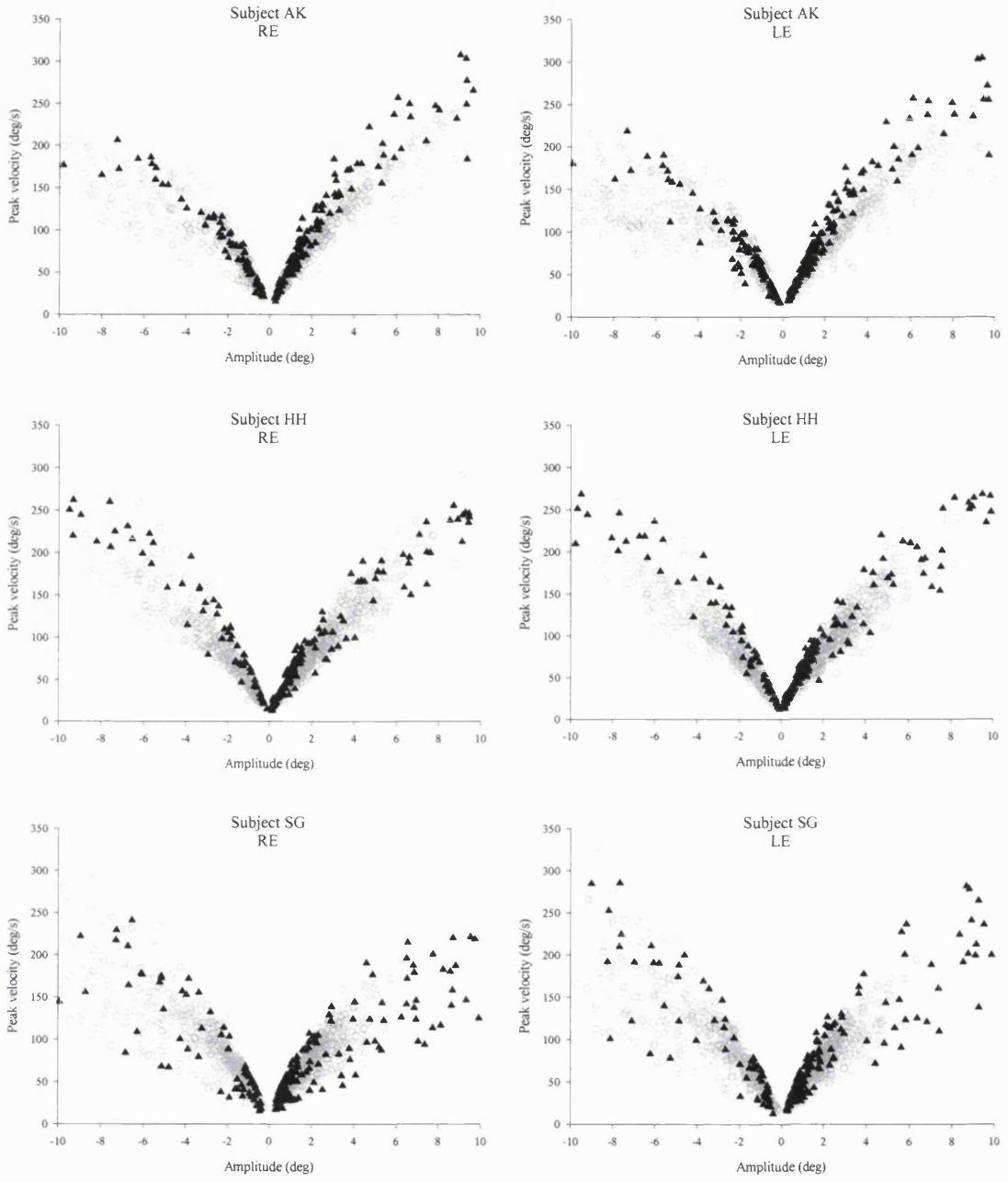


Figure 6.5. Continued

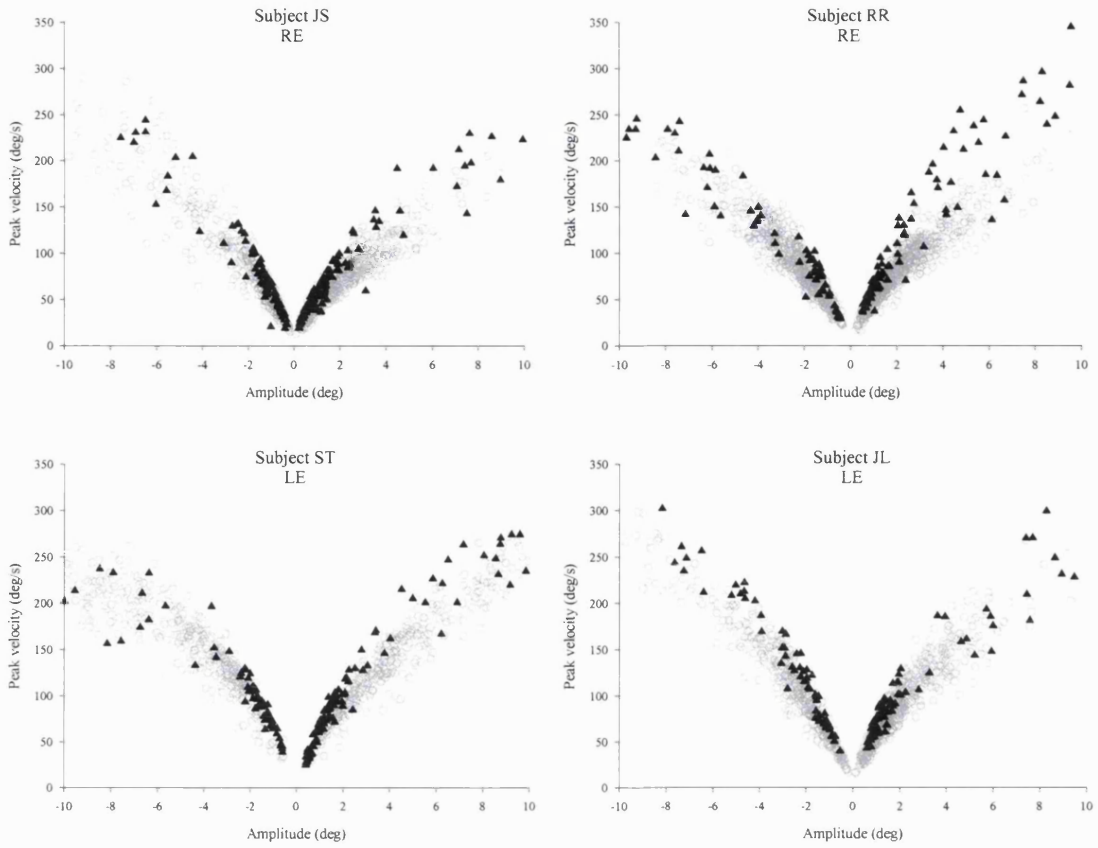


Table 6.4. The main sequence parameters for duration and for peak velocity for vertical saccades and quick phases

		DURATION-AMPLITUDE RELATIONSHIP								PEAK VELOCITY-AMPLITUDE RELATIONSHIP							
		SACCADES				OKN QUICK PHASES				SACCADES				OKN QUICK PHASES			
		UP		DOWN		UP		DOWN		UP		DOWN		UP		DOWN	
		S	I	S	I	S	I	S	I	S	I	S	I	S	I	S	I
RL	RE	0.48	1.38	0.53	1.41	0.35	1.49	0.34	1.51	0.62	1.77	0.60	1.76	0.71	1.63	0.76	1.62
	LE	0.49	1.39	0.52	1.39	0.36	1.50	0.34	1.50	0.63	1.77	0.62	1.77	0.70	1.62	0.70	1.64
AK	RE	0.43	1.40	0.52	1.43	0.55	1.42	0.53	1.42	0.67	1.76	0.56	1.73	0.53	1.72	0.54	1.71
	LE	0.44	1.40	0.52	1.44	0.55	1.41	0.53	1.42	0.67	1.76	0.57	1.72	0.53	1.72	0.54	1.71
HH	RE	0.43	1.41	0.42	1.38	0.33	1.46	0.43	1.45	0.66	1.74	0.69	1.78	0.73	1.67	0.64	1.69
	LE	0.43	1.40	0.42	1.38	0.35	1.45	0.43	1.45	0.66	1.76	0.70	1.78	0.70	1.70	0.65	1.68
SG	RE	0.54	1.48	0.53	1.50	0.42	1.49	0.47	1.45	0.59	1.68	0.59	1.68	0.69	1.65	0.62	1.69
	LE	0.47	1.45	0.48	1.49	0.41	1.49	0.46	1.46	0.66	1.71	0.68	1.67	0.69	1.65	0.63	1.68
JS	RE	0.46	1.43	0.45	1.40	0.44	1.48	0.44	1.42	0.62	1.75	0.64	1.76	0.59	1.66	0.63	1.72
RR	RE	0.43	1.38	0.41	1.41	0.38	1.48	0.36	1.45	0.69	1.80	0.65	1.75	0.67	1.69	0.69	1.70
ST	LE	0.43	1.37	0.51	1.35	0.47	1.40	0.40	1.37	0.65	1.78	0.56	1.82	0.60	1.74	0.60	1.80
JL	LE	0.45	1.36	0.42	1.34	0.38	1.41	0.36	1.41	0.61	1.81	0.64	1.84	0.66	1.75	0.68	1.76
MEAN		**0.46**	**1.40**	**0.48**	**1.41**	**0.42**	**1.46**	**0.42**	**1.44**	**0.64**	**1.76**	**0.63**	**1.76**	**0.65**	**1.68**	**0.64**	**1.70**
±		±	±	±	±	±	±	±	±	±	±	±	±	±	±	±	±
SE		**0.01**	**0.01**	**0.01**	**0.01**	**0.02**	**0.01**	**0.02**	**0.01**	**0.01**	**0.01**	**0.01**	**0.01**	**0.02**	**0.01**	**0.02**	**0.01**

The main sequence parameters for duration and for peak velocity for vertical saccades and vertical OKN quick phases <10° amplitude.
The slope (S) and intercept (I) for the duration-amplitude relation were obtained from a linear regression of the logged main sequence for duration.
The slope (S) and intercept (I) values for the peak velocity-amplitude relation were obtained from a linear regression of the logged main sequence for peak velocity.
Pooled means (±standard error) also shown.

6.3.4 Vertical OKN slow phase gain

In the majority of subjects vertical OKN slow phase gain was either symmetrical in response to upward or downward stimulus motion or, more commonly, there was an asymmetry, with the response to downward motion having a lower gain. Only very occasionally was the response to downward motion greater than the response to upward motion (Table 6.5, 6.6 and 6.7, Figure 6.6). Over all stimulus velocities and spatial frequencies the gain of upward OKN was greater than downward OKN by an average (mean) of 0.08 (standard deviation=0.11, standard error=0.01).

There was a clear decrease in slow phase velocity gain with increasing spatial frequency (Figure 6.7a). Mean slow phase velocity gain values over all stimulus speeds and in both directions were 0.36 at 0.04 cycles/°, 0.30 at 0.08 cycles/° and 0.20 at 0.16 cycles/°.

Slow phase velocity gain also decreased with increasing stimulus velocity (Figure 6.7b). Mean slow phase velocity gain values over all spatial frequencies and in both directions were 0.42 at 10°/s, 0.33 at 20°/s, 0.28 at 30°/s, 0.22 at 40°/s and 0.18 at 50°/s.

Further, there was a general decrease in slow phase velocity gain with increasing temporal frequency (Figure 6.7c). Mean slow phase velocity gain values over all subjects and in both directions were:

0.63 at 0.04Hz, 0.44 at 0.08Hz, 0.35 at 1.2 Hz, 0.28 at 1.6 Hz, 0.20 at 2.0 Hz, 0.32 at 2.4 Hz, 0.24 at 3.2 Hz, 0.21 at 4.0 Hz, 0.19 at 4.8 Hz, 0.18 at 6.4 Hz and 0.17 at 8.0 Hz.

Table 6.5. Vertical OKN gain values - Stimulus with spatial frequency of 0.04 cycles/°

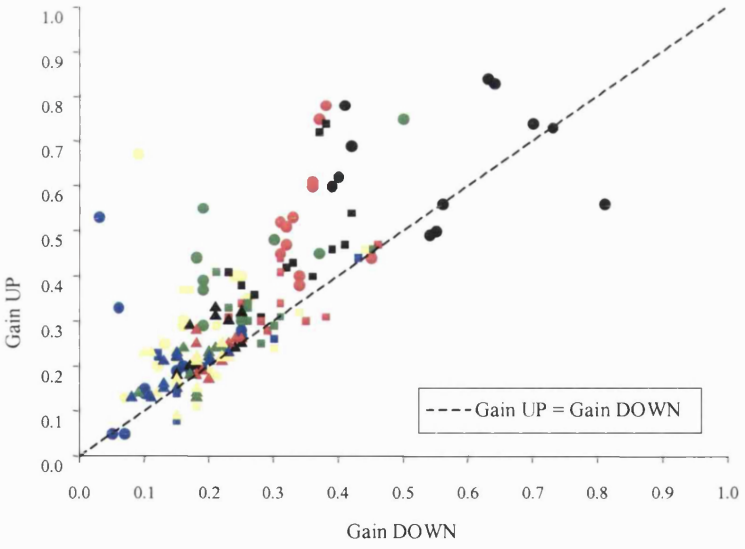
		STIMULUS SPATIAL FREQUENCY = 0.04 cycles/°									
		Upward moving stimulus (°/s)					Downward moving stimulus (°/s)				
		10	20	30	40	50	10	20	30	40	50
RL	RE	0.84	0.52	0.39	0.25	0.33	0.63	0.31	0.19	0.13	0.06
	LE	0.83	0.51	0.37	0.25	0.33	0.64	0.32	0.19	0.13	0.06
AK	RE	0.74	0.61	0.48	0.40	0.27	0.70	0.36	0.30	0.25	0.25
	LE	0.73	0.60	0.48	0.40	0.28	0.73	0.36	0.30	0.24	0.25
HH	RE	0.49	0.38	0.29	0.22	0.15	0.54	0.34	0.19	0.15	0.10
	LE	0.50	0.40	0.29	0.23	0.14	0.55	0.34	0.19	0.15	0.10
SG	RE	0.62	0.47	0.31	0.30	0.19	0.40	0.32	0.25	0.16	0.15
	LE	0.60	0.45	0.30	0.29	0.19	0.39	0.31	0.25	0.16	0.15
JS	RE	0.69	0.53	0.44	0.13	0.05	0.42	0.33	0.18	0.07	0.07
RR	RE	0.56	0.44	0.45	0.35	0.20	0.56	0.45	0.37	0.26	0.16
ST	LE	0.56	0.75	0.75	0.67	0.53	0.81	0.37	0.50	0.09	0.03
JL	LE	0.78	0.76	0.55	0.20	0.05	0.41	0.38	0.19	0.12	0.05
Mean		**0.66**	**0.54**	**0.43**	**0.31**	**0.23**	**0.57**	**0.35**	**0.26**	**0.16**	**0.12**
±		**±**	**±**	**±**	**±**	**±**	**±**	**±**	**±**	**±**	**±**
SE		**0.04**	**0.04**	**0.04**	**0.04**	**0.04**	**0.04**	**0.01**	**0.03**	**0.02**	**0.02**

Table 6.6. Vertical OKN gain values - Stimulus with spatial frequency of 0.08 cycles/°

		STIMULUS SPATIAL FREQUENCY = 0.08 cycles/°									
		Upward moving stimulus (°/s)					Downward moving stimulus (°/s)				
		10	20	30	40	50	10	20	30	40	50
RL	RE	0.74	0.44	0.34	0.37	0.22	0.38	0.31	0.26	0.16	0.12
	LE	0.72	0.44	0.33	0.37	0.23	0.37	0.31	0.26	0.17	0.12
AK	RE	0.43	0.41	0.31	0.32	0.26	0.33	0.31	0.31	0.34	0.30
	LE	0.42	0.41	0.31	0.32	0.26	0.32	0.31	0.31	0.34	0.30
HH	RE	0.47	0.31	0.30	0.19	0.20	0.41	0.38	0.25	0.20	0.19
	LE	0.46	0.30	0.30	0.18	0.21	0.39	0.35	0.26	0.21	0.18
SG	RE	0.38	0.30	0.25	0.23	0.14	0.25	0.28	0.28	0.15	0.15
	LE	0.36	0.28	0.24	0.24	0.17	0.27	0.29	0.30	0.16	0.15
JS	RE	0.41	0.34	0.29	0.24	0.22	0.23	0.31	0.30	0.30	0.12
RR	RE	0.31	0.31	0.33	0.29	0.19	0.28	0.23	0.23	0.21	0.17
ST	LE	0.54	0.47	0.46	0.46	0.44	0.42	0.46	0.45	0.44	0.43
JL	LE	0.40	0.34	0.41	0.11	0.08	0.36	0.25	0.21	0.18	0.15
Mean		**0.47**	**0.36**	**0.32**	**0.28**	**0.22**	**0.33**	**0.32**	**0.29**	**0.24**	**0.20**
±		**±**	**±**	**±**	**±**	**±**	**±**	**±**	**±**	**±**	**±**
SE		**0.04**	**0.02**	**0.02**	**0.03**	**0.02**	**0.02**	**0.02**	**0.02**	**0.03**	**0.03**

Table 6.7. Vertical OKN gain values - Stimulus with spatial frequency of 0.16 cycles/°

STIMULUS SPATIAL FREQUENCY = 0.16 cycles/°											
		Upward moving stimulus (°/s)					Downward moving stimulus (°/s)				
		10	20	30	40	50	10	20	30	40	50
RL	RE	0.33	0.25	0.24	0.23	0.21	0.21	0.18	0.16	0.10	0.13
	LE	0.31	0.28	0.24	0.23	0.21	0.21	0.18	0.16	0.11	0.13
AK	RE	0.24	0.22	0.22	0.22	0.23	0.24	0.22	0.20	0.18	0.15
	LE	0.26	0.21	0.23	0.21	0.22	0.24	0.22	0.20	0.18	0.15
HH	RE	0.30	0.26	0.24	0.22	0.21	0.23	0.24	0.22	0.22	0.20
	LE	0.32	0.26	0.23	0.22	0.22	0.25	0.25	0.23	0.23	0.20
SG	RE	0.22	0.19	0.18	0.17	0.16	0.15	0.19	0.17	0.15	0.13
	LE	0.20	0.17	0.18	0.16	0.15	0.17	0.20	0.17	0.15	0.13
JS	RE	0.18	0.13	0.13	0.09	0.13	0.15	0.18	0.18	0.15	0.08
RR	RE	0.20	0.18	0.14	0.15	0.15	0.18	0.18	0.18	0.18	0.15
ST	LE	0.25	0.25	0.24	0.25	0.23	0.25	0.23	0.21	0.22	0.23
JL	LE	0.29	0.15	0.14	0.14	0.13	0.17	0.13	0.09	0.12	0.11
Mean ± SE		**0.26 ± 0.01**	**0.21 ± 0.01**	**0.20 ± 0.01**	**0.19 ± 0.01**	**0.19 ± 0.01**	**0.20 ± 0.01**	**0.20 ± 0.01**	**0.18 ± 0.01**	**0.17 ± 0.01**	**0.15 ± 0.01**



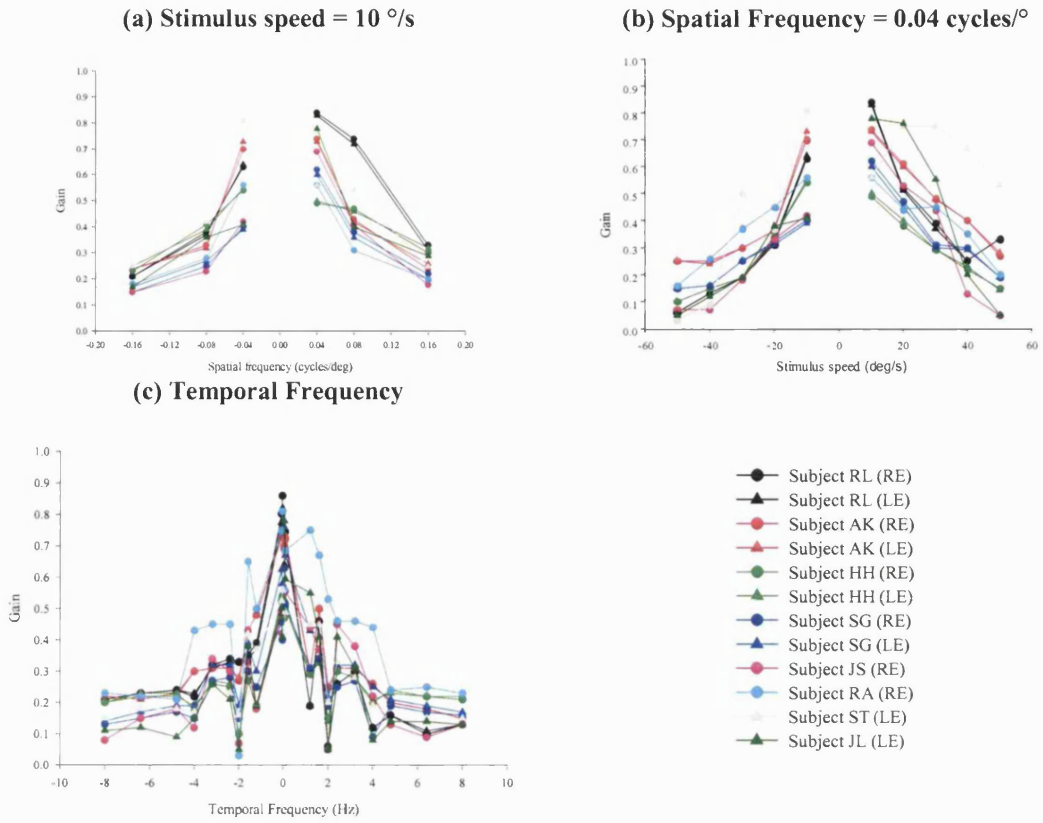
Points above the dotted line indicate that upward gain was greater than downward gain. For points below the line the reverse was true.

Figure 6.6. Upward versus downward OKN gain

Scatter plot of upward slow phase velocity gain against downward slow phase velocity gain in each subject for each stimulus speed and spatial frequency.

- 0.04 cycles/deg at 10 deg/s
- 0.04 cycles/deg at 20 deg/s
- 0.04cycles/deg at 30 deg/s
- 0.04cycles/deg at 40 deg/s
- 0.04 cycles/deg at 50 deg/s
- 0.08 cycles/deg at 10 deg/s
- 0.08cycles/deg at 20 deg/s
- 0.08 cycles/deg at 30 deg/s
- 0.08 cycles/deg at 40 deg/s
- 0.08 cycles/deg at 50 deg/s
- 0.16cycles/deg at 10deg/s
- 0.16cycles/deg at 20 deg/s
- 0.16cycles/deg at 30deg/s
- 0.16cycles/deg at 40deg/s
- 0.16cycles/deg at 50deg/s

Figure 6.7. Vertical slow phase velocity gain dependence on stimulus parameters



(a) Representative plot at a stimulus speed of 10°/s of average vertical OKN slow phase velocity gain plotted against stimulus spatial frequency. (b) Representative plot at a spatial frequency of 0.04 cycles/° of average vertical OKN slow phase velocity gain plotted against stimulus speed. (c) Plot of vertical OKN slow phase velocity gain against stimulus temporal frequency. Negative values represent eye movements downward.

6.4 Discussion

6.4.1 Saccades

A study of a subject's saccades in the four main directions (left, right, up, down) usually reveals pronounced idiosyncratic direction anisotropies (Becker, 1991). It is well established that horizontal centripetal saccades are generally faster than horizontal centrifugal saccades (Frost and Pöppel, 1976; Abel *et al.*, 1979; Jürgens *et al.*, 1981b; Inchingolo *et al.*, 1987; Pelisson and Prablanc, 1988; Collewijn *et al.*, 1988a). However, it is not entirely clear at present whether there are similar consistent

differences between centripetal and centrifugal vertical saccades. Over the range of amplitudes that we elicited (up to 20°) we found no statistical differences between centrifugal and centripetal vertical saccades. Further, there were no statistical differences between upward and downward saccades when centripetal and centrifugal saccades were considered together. Two other studies which used the search coil method also found that upward and downward saccades are similar up to amplitudes of 20° (Yee *et al.*, 1985; Collewijn *et al.*, 1988b). Becker and Jürgens (1990) reported that upward directed 20° target movements elicited higher peak velocities than downward ones but they found that these differences were statistically insignificant. However, the slightly different findings may not be due to methodological differences between the various studies but rather reflects the large range of idiosyncrasies and the small number of subjects investigated in each study (N=5 Yee *et al.*, 1985; N=3 Collewijn *et al.*, 1988; N=10 Becker and Jürgens, 1990).

As discussed in 6.1.1.2 there is disagreement as to whether horizontal and vertical saccades have similar speeds. The dynamics of vertical saccades, as measured by the main sequences for duration and peak velocity, have been variously reported to be the same or slower than those of horizontal saccades. We found that the main sequences for duration and peak velocity of vertical and horizontal saccades have the same basic shape (see Figure 6.1). For both horizontal and vertical saccades, above amplitudes of 4°, duration increased linearly with amplitude. For both directions peak velocity increased exponentially with amplitude. However, although the main sequences of horizontal and vertical saccades had similar shapes, vertical saccades were far *slower* than horizontal ones (see Figure 6.1). Since we found that there were considerable differences in the duration and peak velocity of vertical and horizontal

saccades it appears that they are generated by separate subsystems with different properties.

6.4.2 Comparison of vertical saccades with vertical OKN quick phases

In Chapter 3 we compared the main sequences of horizontal saccades with the main sequences of horizontal OKN quick phases and found that they were very similar. There was no statistically significant difference in the durations of these two eye movements although the differences in peak velocities were statistically significant. In this chapter we compared the main sequences of vertical saccades with the main sequences of vertical OKN quick phases. We are unaware of any other study that has done this. For amplitudes up to 10° qualitatively vertical saccades and vertical OKN quick phases had similarly shaped main sequences for duration and for peak velocity. However, vertical saccades did appear to be slightly faster than vertical OKN quick phases, having shorter durations and reaching higher peak velocities. These differences reach significance if this is assumed at the p=0.05 level (as it has been throughout this thesis).

Although we have shown that there are subtle differences in the speed of fast eye movements depending on how they are elicited, clinical and neurophysiological studies suggest that these differences are unlikely to be of *clinical* significance: -

- In humans lesions in the region of the riMLF lead to a loss of vertical saccades and vertical optokinetic quick phases (case reports summarised by Büttner-Ennever *et al.*, 1982).

- Lesions involving the paramedian pontine reticular formation (PPRF), but sparing the rostral midbrain and riMLF, have also been reported to result in a severe deficit of vertical (and horizontal) saccades and the quick phases nystagmus in humans (Hanson *et al.*, 1986).
- In Niemann-Pick disease Type C the first oculomotor abnormality is a loss of vertical saccades together with an absence of OKN quick phases in the vertical plane (Neville *et al.*, 1973; Shawkat *et al.*, 1994).
- Monkey studies have shown that neurons in the midbrain reticular formation that lie in and around the riMLF exhibit similar activity changes during spontaneous vertical saccades and during the quick phases of vertical OKN but do not respond during the slow phases of vertical OKN or during smooth pursuit (Büttner *et al.*, 1977; King and Fuchs, 1979).
- It has also been shown that in monkeys both upward saccades and upward OKN quick phases are abolished following bilateral lesions of the pretectum including the interstitial nuclei of the posterior commisure (Pasik *et al.*, 1969a; Pasik *et al.*, 1969b; Pasik and Pasik, 1975).
- Downward saccades and OKN quick phases are abolished following bilateral electrolytic lesions of the monkey's midbrain, centred in the riMLF (Kömpf *et al.*, 1979).

These studies all lend support to the concept that vertical saccades and the quick phases of vertical OKN share at least some of the same brainstem neural pathways and are similarly affected by brainstem pathology. Therefore, as with horizontal OKN, in young or uncooperative patients in whom it is not possible to determine a

saccadic main sequence, quantitative evaluation of vertical OKN quick phases may provide a simple and quick reference in vertical saccade slowing.

6.4.3 Vertical OKN slow phase velocity gain

The slow phase velocity gain for vertical OKN is lower than that for horizontal OKN studied in Chapter 3 (although different stimuli were used and therefore this is not a direct comparison). Also vertical OKN gain decreased more steeply as a function of increasing stimulus velocities than horizontal OKN gain (compare Figure 3.4. and Figure 6.7b.). Further, vertical OKN gain displayed more intersubject variability than the horizontal response. We found that the two eyes are well yoked during vertical OKN, but there was a distinct up-down asymmetry. OKN in response to upward stimulus motion had a higher gain than OKN in response to downward stimulus motion. This asymmetry was found at all the stimulus speeds that we used (10-50°/s). Similarly Van den Berg and Collewijn (1989), using the magnetic search coil technique, found that downward OKN had a gain which was lower than upward OKN by about 0.15. This asymmetry was also described by Takahashi *et al.* (1979) and Ogino *et al.* (1996). Interestingly, a similar up-down asymmetry has been found in other frontal-eyed animals (monkey (Cohen *et al.*, 1977; Takahashi and Igarashi, 1977; Igarashi *et al.*, 1978; Matsuo and Cohen, 1984; Himi *et al.*, 1988; Himi *et al.*, 1990); cat (Collins *et al.*, 1970; Vital-Durand and Jeannerod, 1974; Evinger and Fuchs, 1978; Darlot *et al.*, 1981; King and Leigh, 1982)).

Therefore, it appears, that in frontal-eyed animals such as humans there is an asymmetry of vertical OKN with a greater response being evoked by stimulation in an upwards direction. During forward movement flow-fields in frontal-eyed animals are composed of flow lines in which the predominant asymmetries are in the vertical

domain. Thus, when a frontal-eyed animal moves forward while looking straight ahead it is necessary to prevent the optokinetic reflex from rotating the eyes downward in response to optic flow of the highly textured ground plane. Stereopsis cannot stabilise the centrifugal optic flow pattern, therefore it has been suggested (Murasugi and Howard, 1989) that such animals develop an upward preponderance of OKN in order to dampen the influence of the prominent downward optic flow which is present in the lower visual field (i.e. the part of the field which contains the greater richness of visual information). Thus the lower sensitivity of the OKN system to downward motion in frontal-eyed animals most likely compensates in part for the visual dominance of the lower field (Skrandies, 1987) and allows for better stabilisation of the visual field during forward locomotion. Therefore, the asymmetrical response of vertical OKN in cat, monkey and man may be considered as a form of adaptive compensation in the evolution of the vertical optokinetic system.

On the other hand the rabbit, whose eyes are placed low but lateral, shows little directional difference in vertical OKN, although non-horizontal responses are limited to very low velocities (about 1°/s). In lateral-eyed animals visual flow fields generated during forward locomotion show a marked asymmetry of temporal-directed as opposed to nasal-directed optic flow (Gibson, 1966). Thus, the large asymmetries in optic flow, and in OKN, for lateral eyed animals are almost entirely in the horizontal domain.

The finding that the gain of OKN in response to upward stimulus movement in the cat and monkey are higher than those in response to downward stimulus movement, and moreover that this upward preponderance is greatest at higher stimulus velocities (Matsuo and Cohen, 1984; Grasse and Cynader, 1988) is consistent with what is known about the response properties of cells in the lateral

terminal nucleus (LTN) of the accessory optic system. Neurones in the LTN of the cat and monkey have large receptive fields and respond best to large textured stimuli moving in a vertical direction (Grasse and Cynader, 1984; Mustari *et al.*, 1988) and the LTN is considered to be a primary relay station for vertical OKN (Simpson *et al.*, 1979). Single cell recordings in the LTN of the cat have shown that there are about equal numbers of neurons sensitive to upward and downward motion (Grasse and Cynader, 1984) but that cells sensitive to upward motion are tuned to higher velocities than cells sensitive to downward motion (Grasse *et al.*, 1984). In the LTN of the monkey, however, the majority of neurons are tuned to the upward direction (Mustari *et al.*, 1988). In both cat and monkey the range of velocity preferences observed in the LTN is very similar to the range of velocities which elicit OKN (Grasse *et al.*, 1984; Mustari *et al.*, 1988).

6.5 Conclusion

In this chapter vertical saccades were quantitatively compared with horizontal saccades and with vertical OKN quick phases. We also examined the slow phases of vertical OKN.

There were no significant differences in the durations or peak velocities of upward and downward saccades for amplitudes up to 20°. On the other hand, vertical saccades were significantly slower than horizontal saccades. Further we found that vertical OKN quick phases were significantly slower than vertical saccades.

Vertical OKN had a lower slow phase velocity gain compared to that we reported in Chapter 3 for horizontal OKN and there was a distinct up-down asymmetry in vertical OKN. OKN in response to upward stimulus motion had a

higher gain than OKN in response to downward stimulus motion. Thus, only when the response is grossly asymmetric should clinical significance be attached to the finding.

Chapter 7 – Abnormal Vertical Optokinetic Nystagmus

7.1 Introduction

Clinical assessment of eye movement disorders often includes examination of horizontal OKN but not vertical OKN and consequently little is known about vertical OKN in patients with visual system pathology.

This chapter concerns two experiments:-

(1) The purpose of the first experiment was to determine if testing vertical OKN has a role in the clinical assessment of infants and children. In this experiment we identified, by observation of eye movements, abnormal vertical OKN in a number of infants and children. These patients were subsequently shown to have a neurometabolic disease or a brain abnormality.

(2) The purpose of the second experiment was to determine if individuals with disorders of ocular alignment also show abnormalities of vertical OKN. In this experiment the slow phases of vertical and horizontal OKN in a small sample of patients with strabismus were studied and compared with the slow phases of control subjects.

7.1 Experiment 1: Abnormal vertical optokinetic nystagmus in infants and children

7.2.1 Introduction

Horizontal OKN has been studied extensively and is considered to have a valid role in the clinical assessment of infants and children. Testing horizontal OKN is useful in identifying lesions that affect the horizontal optokinetic pathway (involving the cortex, brainstem or cerebellum). A unilateral lesion of this pathway will result in poorer horizontal OKN to the same side as the lesion (Baloh *et al.*, 1977). A complete absence of horizontal OKN can indicate a bilateral lesion affecting the horizontal optokinetic neural pathway. Horizontal OKN testing is also useful in the identification of horizontal saccade initiation failure (HSIF) or 'ocular motor apraxia'. Traditionally HSIF has been diagnosed by recognition of head thrusting and/or synkinetic blinking but, as these compensatory behaviours are not always adopted, identification of absent horizontal OKN quick phases is considered to be a more reliable test for HSIF (Harris *et al.*, 1996b).

Vertical OKN has not been extensively studied and therefore abnormalities in the vertical optokinetic response are not as well understood. Before assessing vertical OKN quantitatively in infants and children we considered those patients with abnormal responses that were so gross that they could be detected simply by observation.

7.2.2 Methodology

7.2.2.1 Subjects

As part of a standard eye movement protocol, vertical OKN was tested in 144 infants and children referred to the Eye Movement Laboratory at Great Ormond Street Hospital. These children were referred from the Ophthalmology, Metabolic and Neurology Departments over a period of one year. Reasons for referral included unusual eye movements, unusual head movements, visual unresponsiveness or the suspicion of a neurometabolic disease.

7.2.2.2 Visual stimuli

The OKN stimulus (see Chapter 2 – Figure 2.3) consisted of alternating black-and-white stripes; horizontal stripes moved vertically to elicit vertical OKN and vertical stripes moved horizontally to elicit horizontal OKN. The grating had a spatial frequency of 0.04 cycles/°, moved at a velocity of 28°/s and was viewed with both eyes open.

The OKN stimulus was rear-projected onto a semi-translucent tangent screen at a viewing distance of 60 cm. This screen subtended 108° of the horizontal visual field and 90° of the vertical visual field. The children sat in a hydraulic chair facing the screen, their eyes level with its centre. Older children sat alone, younger children sat on a parent's lap. The head was immobilised by a headrest or was held by the parent or the examiner.

Horizontal and vertical OKN were tested in each child and OKN was recorded as present, absent or lock-up in the direction of stimulus movement. Lock-up identified cases of saccade initiation failure (SIF). In SIF the quick phases of OKN are

intermittently missed and so the unchecked slow phase drives the eyes to the mechanical limit of gaze where they remain 'locked up' unless a quick phase eventually occurs. Lock-up in response to an upward moving stimulus indicates a saccade initiation failure of down saccades and lock-up in response to a downward moving stimulus indicates a saccade initiation failure of up saccades.

7.2.3 Results

In 118 of the 144 children tested a response to an upward and a downward moving optokinetic stimulus was observed with no evidence of lock-up. These children were considered to have "normal" vertical OKN, although their eye movements were not recorded quantitatively and therefore any subtle differences in the response elicited by an upward compared to that elicited by a downward moving stimulus would not have been detected. The remaining twenty-six children (twelve males and fourteen females) had obviously abnormal vertical OKN. Of these, thirteen had a vertical SIF (VSIF) (in either direction, up/down or in both) and thirteen had absent vertical OKN (in either direction, up/down or in both).

Nine of the children with VSIF had a neurometabolic disease (two had Niemann-Pick disease type C, five had Gaucher disease type 3, one had Gaucher disease type 2 and one had Gaucher disease type 1). The remaining children with a VSIF had an abnormality identified by a magnetic resonance imaging (MRI) scan of the brain.

In eleven of the children with absent up and/or down vertical OKN an MRI scan revealed an abnormality. Of the remaining children in this group one had cerebral palsy and the other had an undiagnosed neurodevelopmental disorder.

All twenty-six of the children with abnormal vertical OKN had vertical and horizontal ocular movements on the doll's head manoeuvre. In all the children with a VSIF vertical smooth pursuit appeared to be normal. In those with a complete absence of OKN, no smooth pursuit could be elicited in any direction. In those with an absence of up vertical OKN, smooth pursuit was absent upwards but present downwards. The reverse was true for those with absent down vertical OKN. Vertical saccades were not formally tested because we have found these very difficult to elicit reliably even in normal children. All children had pupils that were equal and reactive to light apart from one child (P1) who had a dilated right pupil that did not react to light.

Table 7.1. Summary of findings of patients with abnormal vertical optokinetic nystagmus

P	Sex	Age	Up	Dn	L	R	MRI results / diagnosis
1	M	10y7m	LU	+	+	+	MRI- Midline abnormality of the midbrain, periaqueductal gray matter, symmetrical abnormality of dorsal pons. Symmetry of the lesions favours a metabolic disorder.
2	F	7y6m	LU	LU	+	+	MRI- Bilateral occipital infarcts, right frontoparietal lesion. Haemorrhagic ischaemic infarct following mild birth asphyxia.
3	M	7y9m	LU	LU	+	+	Niemann-Pick disease Type C.
4	F	14y	LU	LU	+	+	Niemann-Pick disease Type C.
5	F	8y5m	LU	LU	+	+	Gaucher disease Type 1. MRI- Haemorrhagic lesion in the rostral midbrain of unknown aetiology.
6	F	0y9m	LU	LU	LU	LU	Gaucher disease Type 2.
7	F	5y5m	LU	LU	LU	LU	Gaucher disease Type 3.
8	F	10y9m	LU	+	LU	LU	Gaucher disease Type 3.
9	F	4y7m	LU	+	LU	LU	Gaucher disease Type 3.
10	F	3y10m	LU	+	LU	LU	Gaucher disease Type 3.
11	F	4y1m	+	LU	LU	LU	Gaucher disease Type 3.
12	M	4y9m	+	LU	LU	LU	MRI- Dysmorphic basal ganglia, small corpus callosum, underdeveloped brainstem, particularly the pons.
13	F	2y5m	LU	LU	--	--	MRI- Generalised decrease in bulk of the brain and delay in maturation of myelin.
14	F	5y11m	+	--	+	+	MRI- Abnormality in right cerebellar white matter, right cerebellar peduncles and the right medulla. Appearances consistent with acute inflammatory or neoplastic lesion.
15	F	2y	--	+	+	+	MRI- Dilation of the whole ventricular system, due to hydrocephalus.
16	M	3y	--	+	+	+	MRI- Lesion within the medial thalamic nuclei. Aetiology not known, possibly a metabolic disorder or post-viral encephalitic damage.
17	F	8y9m	+	--	+	+	MRI- Bilateral symmetrical abnormality in upper part of the cerebral peduncles extending into the lower parts of the thalami on both sides. Leigh disease.
18	M	2y2m	--	--	LU	--	MRI- Discrete white matter lesions, lesions in basal ganglia and abnormality in the thalamus on both sides. Aetiology not known, possibly due to atypical infection.
19	M	1y7m	--	--	LU	+	MRI- Incomplete cerebellar and dorsal pontine myelination, marked maturational delay.
20	M	1y	+	--	LU	--	MRI- Cerebellar vermis hypoplasia, increased prominence of superior cerebellar peduncles. Joubert syndrome.
21	M	2y6m	--	--	--	--	MRI- Absent cerebellar vermis, arachnoid cyst in the left posterior fossa. Joubert syndrome.
22	M	6y2m	--	--	--	--	MRI- Multiple cerebral infarcts, due to ante-natal thrombosis of aorta. Cortical blindness.
23	M	5y5m	--	--	--	--	MRI- White matter changes adjacent to posterior aspect of lateral ventricles, abnormality at cerebellar pontine angle. Appearances consistent with degeneration/demyelination.
24	M	4y10m	--	--	--	--	MRI- Lesion in the brainstem near the IIIrd nerve nucleus. Focal ischaemia most likely aetiology.
25	M	16y7m	--	--	--	--	Cerebral palsy. No MRI.
26	F	1y7m	--	--	--	--	Undiagnosed neurodevelopmental disorder. MRI- No abnormality.

P: patient; y: years; m: months; Up: response to an upward moving optokinetic stimulus; Dn: response to a downward moving optokinetic stimulus; L: response to a leftward moving optokinetic stimulus; R: response to a rightward moving optokinetic stimulus; +: OKN present, --: OKN absent; LU: lock-up.
The first 13 patients listed are those with a vertical saccades initiation failure (in either direction, up/down, or both). The final 13 patients listed had absent vertical OKN (in either direction, up/down or both).

7.2.4 Discussion

First we will consider the children with VSIF – that is, lock-up on vertical OKN testing and thus an absence of upward and/or downward quick phases and discuss the most relevant cases. The riMLFs, part of the midbrain reticular formation, are known to be crucial for the generation of vertical saccades and thus probably optokinetic quick phases. Experimental lesions and clinicopathological studies suggest that from the midbrain reticular formation the efferent fibres for vertical saccades/optokinetic quick phases and those for vertical smooth pursuit travel together to the vertical oculomotor nuclei (Büttner-Ennever *et al.*, 1982; Pierrot-Deseilligny *et al.*, 1982). All the children described in this study with VSIF had normal vertical smooth pursuit and therefore their VSIF is most likely to be the result of a lesion of the riMLFs themselves or afferent fibres to them. This is consistent with an abnormality of the midbrain, periaqueductal gray matter and dorsal pons identified in one child (P1) and with an underdevelopment of the brainstem in another (P12).

Nine of the children identified with VSIF in this study had a neurometabolic disease (this relatively large number of children with a neurometabolic disease and VSIF reflected the pattern of patients referred to our laboratory). Two children (P3 and P4) with VSIF were diagnosed as having Niemann-Pick Disease type C. Deficits in the generation of rapid vertical eye movements are frequently seen in cases of Niemann-Pick type C (Sanders and Wybar, 1969; Neville *et al.*, 1973) and indeed VSIF may be the presenting sign of the disease (Shawkat *et al.*, 1994), as was the case with one child (P4) reported here. Neville and co-workers (Neville *et al.*, 1973) described the typical sequence of oculomotor abnormalities seen in Niemann-Pick disease. This begins with loss of vertical saccades and absence of OKN quick phases (particularly affecting down gaze), followed by impairment of vertical smooth pursuit.

Next the velocity of saccades to voluntary and optokinetic stimuli is reduced and finally convergence is affected. The two patients reported in our study were thought to be in the early stages of the disease since only their vertical saccades and optokinetic quick phases (both up and down) were affected. Vertical smooth pursuit, horizontal saccades, horizontal OKN and convergence were all intact.

Rottach *et al.* (1997) recorded oblique saccades in three sisters with Niemann-Pick type C disease. They found that the time from onset to peak velocity was similar for both the horizontal and vertical components. However, the horizontal peak velocity was much greater and as a result the initial trajectory of the oblique saccades was almost horizontal. Rottach *et al.* suggest that although the horizontal burst neurons in the PPRF and the vertical burst neurons in the riMLFs came on at the same time, the output of the latter was weak and conclude that it seems likely that the burst cells of the riMLF are directly affected by Niemann-Pick type C disease.

The oculomotor abnormalities in neuronopathic Gaucher disease (GD3) have been outlined by Harris and colleagues (Harris *et al.*, 1999) and these include HSIF, strabismus, slow horizontal and downward saccades and an abnormal VOR. HSIF is the most consistent finding and is frequently the first sign of neurological involvement. In our experience, when there is dysfunction of supranuclear ocular motor control in Gaucher disease, horizontal gaze is always affected first and thereafter involvement of vertical eye movements may indicate progression of the disease. Therefore we were surprised to find that one child (P5) had VSIF but normal horizontal OKN. However, an MRI scan revealed a lesion in the rostral midbrain with the appearance of an old haemorrhage. This was thought to be the cause of the VSIF, not Gaucher disease. Thus, despite the identification of VSIF her current diagnosis is of GD1 (that is, the non-neuronopathic form), although she is still under investigation.

Of the thirteen cases of VSIF identified in this study, seven had HSIF. HSIF has been associated with a wide range of conditions (Harris, 1997) but is frequently found to be idiopathic. Of the thirteen cases of VSIF identified in this study *none* were idiopathic. Thus, the presence of VSIF, whether associated with HSIF or not, should always indicate investigations for a more sinister cause. Equally, identification of HSIF should lead to testing of vertical OKN.

A VSIF will not necessarily involve both upward and downward saccades. It has been suggested that saccades may be lost in only one vertical direction because burst neurons for upward and downward saccades are topographically arranged within the riMLFs. However, investigators have reached differing conclusions regarding the exact distribution of up- and down-burst neurons within the riMLF. Some investigators have suggested that neurons in the riMLFs projecting to muscles that depress the eye may be located more rostrally, whereas projections to muscles that elevate the eye lie more caudally (Kömpf *et al.*, 1979; Wang and Spencer, 1996). On the other hand, Büttner-Ennever and colleagues (Büttner-Ennever *et al.*, 1982) suggested that the medial aspect of the riMLFs contains neurons involved in upgaze while neurons from the lateral portion are primarily involved in downgaze, but Pierrot-Deseilligny *et al.* (1982) reached opposite conclusions regarding the arrangement of vertical burst neurons within the riMLFs. In neurometabolic diseases it appears that downward saccades are often affected before upward saccades. This has been observed in Niemann-Pick disease (Neville *et al.*, 1973) and in Gaucher disease (Harris *et al.*, 1999) and was evident in the children with Gaucher disease type 3 in this study.

Next we will consider the thirteen children with absent vertical OKN – that is, those with no response to an upward and/or downward moving optokinetic stimulus.

As discussed in Chapter 1 the vertical OKN neural pathways most likely involve the cortex, brainstem and cerebellum. In one child (P22) with a complete absence of vertical OKN there was cortical involvement. In six of the children with absent up and/or down vertical OKN an abnormality that specifically involved the brainstem and/or cerebellum was identified by MRI scan (P14, P19, P20, P21, P23, P24). Patient 14 was reported to have an abnormality of the right medulla and cerebellum, Patient 19 had incomplete cerebellar and dorsal pontine myelination and Patient 23 had an abnormality at the cerebellar pontine angle. Patient 24 had a complete absence of vertical OKN and was also found to have an internuclear ophthalmoplegia and partial third nerve palsy. An MRI scan showed a lesion in the brainstem near the third nerve nucleus. As the third nerve nucleus lies partly within the MLF (see Figure 1.3) the clinical findings are consistent with the results of the scan. Patient 20 and 21 had a diagnosis of Joubert syndrome. Oculomotor abnormalities have previously been reported in association with Joubert syndrome (Moore and Taylor, 1984; Lambert *et al.*, 1989) and it is believed that they are due to dysfunction of both the cerebellum and the brainstem (Lambert *et al.*, 1989).

Four children with absent up and/or down vertical OKN had a lesion that most probably involved the rostral midbrain (P15-18). Patient 15 had hydrocephalus and dilation of the whole ventricular system and it is likely that the rostral midbrain was affected by dilation of the third ventricle. Three children (P16, P17, and P18) had lesions that involved the thalamus. Although there have been reports of thalamic lesions affecting vertical gaze (Kobari *et al.*, 1987; Lazzarino and Nicolai, 1988; Fensore *et al.*, 1988; Ghidoni *et al.*, 1989) there is no anatomical documentation for thalamic control of vertical gaze. Therefore, it is possible that in these three cases

there was a disruption of the pathways controlling vertical gaze in the adjacent rostral midbrain.

Although the vertical OKN pathways have not been fully elucidated it has been proposed (Pierrot-Deseilligny *et al.*, 1982) that the tracts involved in upgaze decussate through the posterior commissure, while those for downgaze do not pass through the commissure and possibly decussate near the oculomotor nuclei. Since we found that vertical OKN may be absent in only one direction, there clearly is some segregation between the neural pathways for up vertical OKN and those for down vertical OKN. However, from the results of MRI scans alone it is not possible for us to reach any conclusions regarding the extent to which these pathways are separate.

Of the twenty-six children with abnormal vertical OKN (VSIF and absent vertical OKN) in this study, nine (P1-5 and P14-17) had normal horizontal OKN and of these children six (P1, P2, P5, P15, P16 and P17) had a lesion that most probably specifically involved the rostral midbrain. Thus, it appears that abnormal vertical OKN but normal horizontal OKN is suggestive of a rostral midbrain lesion. Our study demonstrates that vertical OKN testing *in addition* to horizontal OKN testing does indeed have a useful role in the detection of neurological abnormalities in infants and children.

7.3 Experiment 2: Disorders of vertical OKN in patients with ocular misalignment

7.3.1 Introduction

Despite the findings of the previous experiment we are aware that neurological abnormalities may not be the only cause of abnormal vertical optokinetic responses. As discussed in Chapter 1, a substantial body of research has documented an asymmetry in the monocular horizontal OKN response in human subjects who have had normal visual development interrupted early in life. Thus, before we use vertical OKN in our clinical assessment of the oculomotor system we need to establish whether vertical OKN is also abnormal in patients who have had a disruption to binocular vision.

Vertical OKN responses in human subjects lacking binocular vision have not been well defined. Schor and Levi (1980) reported reduced velocity of responses to upward optokinetic stimuli presented monocularly to a group of individuals with strabismic and anisometropic amblyopia. This report has received some recent support (Proudlock *et al.*, 2001). On the other hand, Tychsen *et al.* (1984) reported that patients with early onset strabismus showed reductions of bi-ocular vertical OKN in response to downward stimulus motion, whereas clinically similar patients whose strabismus was of later onset did not show a marked vertical asymmetry of OKN.

As a preliminary study, we assessed the optokinetic responses of a small group of patients with misalignment of their visual axis from childhood.

7.3.2 Methodology

This experiment was conducted in the Ocular Motor Neurophysiology Laboratory at the Department of Veterans Affairs Medical Centre, Case Western Reserve University, Cleveland, USA. Therefore, the patients studied were adults and the equipment was the same as that described in the Chapter 6 (also see Figure 2.2). We measured eye movements using the magnetic search-coil technique (see Chapter 2).

7.3.2.1 Subjects

We studied six patients with misalignment of their visual axes since childhood. Clinical details are summarised in Table 7.2. In four of the patients (P1-4) the presence of dissociated vertical deviation (DVD) and manifest latent nystagmus in association with strabismus suggested an early onset, although no formal records were available. Patient 5 reported that his strabismus had been present from a very early age. Three patients (P1, P2, P5) had some degree of amblyopia. Patient 4 had intermittent strabismus throughout childhood that, when she was in her teens, became symptomatic as episodes of left esotropia with pupillary constriction. She had normal distance vision and preserved stereopsis. Four patients (P1, P2, P4, P6) had undergone recent surgery to correct strabismus. One amblyopic patient (P5) had undergone resection of a low-grade cerebellar astrocytoma. This left him with a large midline defect that involved the fastigial nucleus. Patient 6 had apparently experienced normal binocular vision until aged 12 years when he suffered eye trauma. A cataract developed and was removed 18 months later. Although he was fitted for a contact lens on that eye, he did not wear it. From then until age 35 years, when an artificial lens

was implanted, he had defocused vision. After the lens implant, he noted variable diplopia and abnormal motion of vision in his left eye that he could not control. He underwent strabismus surgeries on his left eye at ages 38 and 39 to correct exotropia, but these were only temporarily successful. We also studied eight control subjects, aged between 24 and 54 years. All subjects and patients gave informed, written consent.

7.3.2.2 Visual Stimuli

The OKN stimulus was rear-projected onto a semi-translucent tangent screen at a viewing distance of 1 m. The stimulus screen subtended 72° horizontally and 60° vertically (see Figure 2.2). The stimulus consisted of alternating black-and-white stripes with a spatial frequency of 0.04 cycles/°. The visual stimuli moved at 22.5 and 12°/s for 20s, first up, then down, then to the left and then to the right. The screen was blanked for 10s between stimuli. Each sequence of stimuli was viewed first with both eyes, then with the right eye (left occluded) and, finally, with the left eye (right occluded). Subjects were instructed to keep gazing into the centre of the pattern, to try to maintain optimal clarity of the stripes and not to deliberately follow any one stripe.

7.3.2.3 Data Analysis

The computer program described in Chapter 2 was used to determine the OKN slow phase velocity at each stimulus speed. We analysed separately data from each eye during right-eye, left-eye, or bi-ocular stimulation.

Table 7.2 Summary of clinical findings of patients with ocular misalignment

P	Sex	Age^	Visual Acuity* /Stereopsis+	Current Ocular Alignment	Nystagmus#	Other Information
1	F	54	6/9 RE; 6/24 LE; Absent stereovision	15° left exotropia; left DVD	MLN	No operations
2	F	49	6/7.5 RE; 6/60 LE; Absent stereovision	6° left esotropia; right DVD	MLN	Originally esotropic; 3 operations LE; exotropic age 17-44; esotropic since operation 2001
3	F	31	6/7.5 RE; 6/7.5 LE; Absent stereovision	3° right esotropia; bilateral DVD	MLN	Esotropia, originally intermittent, became sustained with diplopia on distance fixation during teens. Operation 2001 RE corrected it
4	F	18	6/7.5 RE; 6/9 LE; 50" of stereovision	Intermittent 3° left esotropia; right DVD	MLN	Recession right superior rectus 1998; recession right medial rectus 1999; Intermittent vergence spasms with constriction of L pupil
5	M	51	6/9 RE; CF LE; Absent stereovision	6° left esotropia	MLN	Life-long strabismus and left amblyopia; Midline cerebellar defect following resection of tumour 1995
6	M	40	6/6 RE; 6/7.5 LE; Absent stereovision	3° left esotropia; variable left hypertropia	Slow vertical drifts of left eye	Lost left lens in trauma at age 12; Lens implant age 35; Surgeries at ages 38 and 39 to correct exotropia

P: patient; RE: right eye; LE: left eye; L: left; R: right; CF: counting fingers; DVD: dissociated vertical deviation, MLN: manifest latent nystagmus.
^ Ages are in years; * Corrected Snellen visual acuity tested at 6 m; + Stereopsis at 40 cm viewing Titmus test; # Spontaneous nystagmus during attempted fixation (neither eye occluded).

7.3.3 Results

7.3.1 Vertical OKN slow phase gain

As in the experiment in Chapter 6, in the normal subjects, during bi-ocular and monocular viewing, vertical OKN gain was usually asymmetrical with the response to downward motion having a lower gain (up-down asymmetry). The gain values recorded from the normal subjects in the current experiment were not significantly different from those recorded in Chapter 6 (see Table 6.5).

In four patients (P1, P2, P4, P5) vertical OKN gain, to one stimulus at least, was significantly less than that for our control subjects. Vertical OKN asymmetries were evident in all of our patients and these asymmetries at times exceeded the 95% confidence intervals for our control subjects (Table 7.3, 7.4). An up-down asymmetry was the most common finding in the patients. However, down-up asymmetries (the upward response having a lower gain than the downward response) were also evident but these asymmetries were statistically significant in only one patient (Patient 4, viewing a stimulus moving at 22°/s with her right eye). The direction of the asymmetry (up-down or down-up) could vary according to the speed of the stimulus or according to whether the patient was viewing with both eyes, with his right eye or with his left eye. As up-down and down-up asymmetries occurred in both strabismic and non-strabismic eyes, the direction of the asymmetry did not appear to be related to which eye was deviating. However, a down-up asymmetry did occur more frequently when the patients viewed the stimulus at the higher speed.

Table 7.3. Vertical bi-ocular OKN gain values

Patient		Up 12°/s	Dn 12°/s	Up 22.5°/s	Dn 22.5°/s	Up-Dn 12°/s	Up-Dn 22.5°/s
1	RE	0.58	0.60	0.33	0.37	-0.02	-0.03
	LE	0.78	0.46	0.38	0.32	0.32*	0.06
2	RE	0.65	0.49	0.61	0.55	0.16	0.06
	LE	0.62	0.41*	0.58	0.57	0.21	0.01
3	RE	0.73	0.69	0.62	0.54	0.04	0.08
	LE	0.65	0.67	0.54	0.55	-0.02	-0.01
4	RE	cb	cb	0.24	0.16	cb	0.08
	LE	0.11*	0.00*	0.17	0.11	0.11	-0.06
5	RE	0.65	0.60	0.53	0.53	0.05	0.00
	LE	0.49	0.46	0.36	0.35	0.03	0.01
6	RE	cb	cb	0.86	0.65	cb	0.21
	LE	0.87	0.62	0.86	0.65	0.25*	0.21
NS	RE	0.70±0.04	0.61±0.03	0.50±0.08	0.39±0.06	0.09±0.03	0.11±0.05
	LE	0.71±0.04	0.64±0.04	0.50±0.08	0.43±0.07	0.07±0.03	0.07±0.05

Table 7.4. Vertical monocular OKN gain values

Patient		Up 12°/s	Dn 12°/s	Up 22.5°/s	Dn 22.5°/s	Up-Dn 12°/s	Up-Dn 22.5°/s
1	RE	0.62	0.41	0.21	0.20	0.21	0.01
	LE	0.72	0.67	0.18*	0.29	0.05	-0.11
2	RE	0.47	0.29	0.42	0.47	0.18	-0.05
	LE	0.70	0.41	0.54	0.27	0.29*	0.27*
3	RE	0.71	0.51	0.61	0.53	0.20	0.08
	LE	0.80	0.67	0.62	0.40	0.13	0.22
4	RE	cb	cb	0.07*	0.23	cb	-0.16*
	LE	0.25	0.13*	0.17*	0.07*	0.12	0.10
5	RE	0.64	0.53	0.34	0.21	0.11	0.13
	LE	0.40	0.14*	0.30	0.10*	0.26*	0.20
6	RE	cb	cb	0.82	0.65	cb	0.17
	LE	0.97	0.69	0.79	0.67	0.28*	0.12
NS	RE	0.66±0.06	0.60±0.06	0.52±0.07	0.42±0.05	0.06±0.03	0.10±0.04
	LE	0.64±0.07	0.61±0.07	0.55±0.05	0.48±0.07	0.03±0.02	0.07±0.03

RE: right eye; LE: left eye; Up: upward moving stimulus; Dn: downward moving stimulus; cb: connection on scleral search coil broke during this part of the experimental session; *: value exceeded 95% confidence interval for normal subjects; Up-Dn: Difference between upward and downward gain, positive values indicate that upward gain was greater than downward gain and negative values indicate that downward gain was greater than upward gain.
Data are means from viewing eye; for normal subjects (NS) data are pooled means (± standard errors).

7.3.2 Horizontal OKN slow phase gain

For the control subjects a clear preference for right-to-left or left-to-right stimulation during bi-ocular or monocular stimulation was absent.

One patient (P1) demonstrated a substantial nasal-to-temporal (N-T) asymmetry during monocular viewing. In this patient the slow phase velocity was significantly greater in response to a nasally moving stimulus (to the left when viewing with the right eye and to the right when viewing with the left eye). Patient 4 also showed a N-T asymmetry, but the gain values were low.

Two patients (P3, P5), during monocular viewing conditions, rather than the classic N-T asymmetry demonstrated a significant bias for one direction of horizontal motion. The same directional bias was also apparent when these patients viewed the stimulus bi-ocularly. Thus, in P3 and P5 gain was significantly greater for leftward moving optokinetic stimuli irrespective of which eye was viewing. Patient 2 also had a directional bias of horizontal OKN with higher rightward gains but this was not statistically significant during monocular viewing.

Paired comparisons of monocular horizontal and vertical optokinetic responses for each patient's eye (Tables 7.4, 7.6) showed substantial variability, and no consistent differences.

Table 7.5. Horizontal bi-ocular OKN gain

Patient		R 12°/s	L 12°/s	R 22.5°/s	L 22.5°/s	R-L 12°/s	R-L 22.5°/s
1	RE	0.72	0.43*	0.20*	0.07*	0.29*	0.13*
	LE	0.82	0.14*	0.20*	0.07*	0.68*	0.13*
2	RE	0.61	0.39*	0.70	0.57	0.22*	0.13*
	LE	0.61	0.38*	0.75	0.55	0.23*	0.20*
3	RE	0.64	0.83	0.63	0.75	-0.19*	-0.12*
	LE	0.55*	0.83	0.69	0.78	-0.28*	-0.09*
4	RE	cb	cb	0.34	0.23*	cb	0.11*
	LE	0.62	0.20*	0.08*	0.19*	0.42*	-0.11*
5	RE	0.50*	0.62	0.16*	0.48	-0.12	-0.32*
	LE	0.57*	0.60	0.18*	0.47	-0.03*	-0.29*
6	RE	cb	cb	0.81	0.88	cb	-0.07*
	LE	0.66	0.59	0.76	0.73	0.07	0.03
NS	RE	0.80±0.05	0.79±0.06	0.66±0.07	0.66±0.06	0.06±0.02	0.03±0.01
	LE	0.81±0.04	0.79±0.05	0.68±0.07	0.66±0.07	0.04±0.01	0.02±0.01

Table 7.6. Horizontal monocular OKN gain

Patient		R 12°/s	L 12°/s	R 22.5°/s	L 22.5°/s	R-L 12°/s	R-L 22.5°/s
1	RE	-0.19*	0.22*	-0.06*	0.18	-0.41*	-0.24*
	LE	0.69	-0.31*	0.40	-0.14*	1.0*	0.54*
2	RE	0.38*	0.35*	0.53	0.49	0.03	0.04
	LE	0.53	0.43	0.45	0.36	0.10	0.09
3	RE	0.64	0.83	0.59	0.80	-0.19*	-0.21*
	LE	0.55	0.78	0.67	0.74	-0.23	-0.07
4	RE	cb	cb	-0.01*	0.04*	cb	-0.05
	LE	0.36	0.13*	0.18	0.12*	0.23	0.06
5	RE	0.21*	0.76	0.22	0.43	-0.55*	-0.21*
	LE	0.00*	0.57	0.09*	0.37	-0.57*	-0.28*
6	RE	cb	cb	0.81	0.86	cb	-0.05
	LE	0.69	0.66	0.81	0.77	0.03	0.04
NS	RE	0.66±0.05	0.71±0.06	0.52±0.08	0.56±0.08	0.05±0.01	0.06±0.01
	LE	0.72±0.07	0.66±0.06	0.62±0.08	0.59±0.08	0.07±0.03	0.04±0.01

RE: right eye; LE: left eye; R: rightward moving stimulus; L: leftward moving stimulus; cb: connection on scleral search coil broke during this part of the experimental session; *: value exceeded 95% confidence interval for normal subjects; R-L: Difference between rightward and leftward gain, for the patient data positive values indicate that rightward gain was greater than leftward gain and negative values indicate that leftward gain was greater than rightward gain.
Data are means from viewing eye; for normal subjects (NS) data are pooled means (± standard errors).

7.3.4 Discussion

In this study an asymmetry of bi-ocularly and monocularly viewed vertical OKN, with upward stimulus motion eliciting a higher gain compared to downward stimulus motion, was the most common finding in both normal subjects and patients. In our patients asymmetries where downward stimulus motion elicited higher gain compared to upward stimulus motion (down-up asymmetries) were also seen, although these asymmetries were rarely significant. Schor and Levi (1980) reported a number of abnormalities in the monocular vertical optokinetic response of adult amblyopes. The most common deficit they noted was a reduced velocity for upward slow phases resulting in a down-up asymmetry. This was observed in both the amblyopic and non-amblyopic eyes of some subjects. Similarly, in a group of sixteen patients with early-onset strabismus, Proudlock and co-workers (2001) reported poor upward gains in the deviating eye of four patients and the non-deviating eyes of six patients. We noted significantly reduced velocities for upward *and* downward slow phases in the deviating and non-deviating eyes of a number of our patients. On the other hand, two patients (P3, P6) had vertical optokinetic responses with a high gain. All the patients in this study had a strabismus and all had amblyopia except for these two patients. Further the strabismus evident in Patient 3 only became sustained in her teens and the strabismus seen in Patient 6 was of late onset following trauma at age 12. Although it is tempting to speculate that lower vertical OKN gains are the result of amblyopia rather than strabismus or are related to the age of the patient at the onset of a sustained deviation, it is impossible for us to draw any conclusions from the small sample that we studied.

A N-T OKN asymmetry was evident in Patient 1 and also in Patient 4, although her gain values were low. In these patients, the monocular T-N response had

slow phases in the normal direction whereas the response to N-T stimulation was in the correct direction, although diminished, or was in the inappropriate direction. This inappropriate response to an optokinetic stimulus moving in the N-T direction has previously been reported in patients with latent/manifest latent nystagmus (LN/MLN) (Milojevic *et al.*, 1967; Tsutsui and Fukai, 1979; Kommerell and Mehdorn, 1982; Dickinson and Abadi, 1990). Further, it has been suggested that subjects with LN/MLN do not have a genuine N-T OKN deficit and that any apparent asymmetry or reversal of monocular OKN might be the result of the summation of the horizontal OKN with the spontaneous oscillation with the latter being changed in some way by the stimulus (Halmagyi *et al.*, 1980; Dickinson and Abadi, 1990).

Three patients (P2, P3, P5) displayed an asymmetry in horizontal OKN that resembled a directional bias (leftward or rightward asymmetry rather than a N-T asymmetry). This is not the typical asymmetry associated with abnormal binocular visual development reported in the literature. We note, however, that in P5 this directional asymmetry could be due to the patient's cerebellar defect and may have disguised any N-T asymmetry.

Our findings regarding horizontal OKN raise some interesting points. Firstly, Patient 4 had 50" of stereopsis but latent nystagmus and DVD were also present. Thus, although lack of stereopsis is commonly associated with latent nystagmus and OKN abnormalities (Gresty *et al.*, 1992) it may not have any pathophysiological role. This view is supported by animal studies (Tusa *et al.*, 2002). Secondly, we only found a significant N-T asymmetry of monocular horizontal OKN in one (P1) of our patients, although five (P1-5) had latent nystagmus. This argues against the theory proposed by Kommerell (1988) that, in early-onset strabismus, latent nystagmus is a

consequence of the persistent N-T asymmetry seen in infants before the development of binocular vision.

7.3 Conclusion

In the first experiment of this chapter we showed that vertical OKN testing does have a useful role in the detection of neurological abnormalities in infants and children. Lock-up, and thus cases of VSIF, and absent vertical OKN can be identified simply by observation but further investigations are required to determine if quantitative recording of eye movements during vertical OKN testing would have additional value.

We found that VSIF was frequently associated with a neurometabolic disease but was also associated with lesions involving the brainstem. Absent vertical OKN was associated with lesions of the cortex, brainstem and/or cerebellum. Abnormal vertical OKN (VSIF or absent vertical OKN) but normal horizontal OKN is suggestive of a rostral midbrain lesion.

In the second experiment of this chapter we examined the monocular and bi-ocular horizontal and vertical optokinetic responses of patients with disturbances of binocular vision since childhood. Horizontal and vertical optokinetic responses in these patients were often poorer than those recorded from control subjects. For vertical OKN the most frequently seen asymmetry was the result of upward OKN gain being greater than downward. However, the patients' responses were very variable. Individuals with disturbances of binocular vision from an early age often show abnormalities of horizontal OKN. The aim of this experiment was to determine if they might also show abnormalities of vertical OKN and it appears that they do.

However, from the small, heterogeneous group of patients that we studied it was not possible to clearly define these abnormalities or to determine what factors cause them.

Chapter 8 – General Discussion and Conclusions

We believe that OKN testing is undervalued as a clinical tool. Thus, the aim of this thesis was to explore the clinical uses of optokinetic testing. To do this we considered the quick and the slow phases of both horizontal and vertical OKN.

8.1 Horizontal OKN

8.1.1 Horizontal OKN quick phases

Significant slowing of saccades is an important clinical finding that can indicate a range of abnormalities. To properly identify patients with slow saccades it is necessary to elicit a large number of saccades over a range of amplitudes. This is impossible to do in infants or unco-operative patients. However, if it could be shown that OKN quick phases and saccades have similar dynamics then it would be possible to assess the speed of OKN quick phases, which are simple to elicit, as a substitute for assessing the speed of saccades.

Our study in Chapter 3 found that horizontal OKN quick phases and horizontal saccades do have similar speeds. We discovered that the main sequence for duration of horizontal saccades is not significantly different from that of horizontal OKN quick phases. Although the main sequence for peak velocity of horizontal saccades is slightly different from that of horizontal OKN quick phases, these differences are so slight that they are unlikely to be of clinical significance.

We obtained similar results using an infrared eye tracker and by electro-oculography and therefore we suggest that electro-oculography would be sufficient for identifying abnormalities in the OKN main sequence. Electro-oculography has the advantages of being readily available, relatively cheap and well tolerated by young infants.

In Chapter 4, we explored further the idea of recording the speed of horizontal OKN quick phases as a substitute for measuring saccade speed. Previously, as very little was known about the speed of normal horizontal saccades in infants, it was not possible to identify with certainty abnormal infant saccades. Thus, in the first study of Chapter 4 we compared the temporal characteristics of infant horizontal OKN quick phases with those of adults. It has been suggested that horizontal saccades in infants may be slower than those of adults (Hainline *et al.*, 1984b; Hainline and Abramov, 1995), however, we found no evidence for slow horizontal quick phases in normal infants. Indeed, in our study, although the differences were not significant, infant horizontal OKN quick phases tended to be *faster* than adult quick phases. The finding that there is no significant difference between adult and infant horizontal OKN quick phases has an important clinical implication: slow horizontal OKN quick phases and horizontal saccades should *always* be considered as abnormal, even in infants as young as 2 months, and when detected should lead to further investigations.

Recordings must be calibrated in order to obtain quantitative information about OKN quick phases. However, it is not necessary to elicit saccades. In order to calibrate our recordings, the infants simply had to fixate between two targets. It was not necessary for the fixation between the targets to be completed in a single saccade and in fact any number of movements could be included. Although, ultimately any calibration method depends on the infant's ability to refixate, we found that with

careful examination of the results this method of calibration was very successful. Video monitoring and recording of infants during testing is essential because during analysis of the results this gives the investigator the opportunity to examine simultaneously the state of the child and the eye movement recording (Jacobs *et al.*, 1992). Therefore, particularly for the calibration, only eye movements when the child is alert, attending the target and not moving can be included in the analysis.

It was necessary, before using horizontal OKN quick phase testing as a clinical tool for identifying slow horizontal saccades, to confirm that horizontal saccades and horizontal OKN quick phases are affected by the same disease processes. To determine this we examined children with Gaucher disease (GD). Patients with GD type 3 (GD3) have slow horizontal saccades and other oculomotor signs which indicate brainstem involvement (Harris *et al.*, 1997). We found that horizontal OKN quick phases were also significantly slowed in these children; the quick phases recorded from the children with GD3 had an increased duration and lower peak velocity compared to the control subjects. The fact that both the duration and the peak velocity of horizontal saccades and horizontal OKN quick phases are affected in a similar way in brainstem pathology provides further evidence that these eye movements share at least some of the same neural circuitry.

The ability to identify slow saccades in infants and children with GD has considerable implications for their management. GD without neurological involvement (GD1) is treatable with exogenous enzyme replacement therapy (ERT). Unfortunately, ERT does not halt the fatal neurological progression of type 2 (infantile) disease (GD2). However, ERT can slow down or possibly halt the neurological progression in GD3, but higher doses are required. Therefore, so that appropriate treatment can be given, it is essential to distinguish between GD1 and

GD3. ERT slows down the progression of neurological disease in GD3, but it is not possible to revert neurological damage once it has occurred. This means that early detection of neurological abnormalities is very important. It has been found that SIF is often the earliest neurological sign of GD3 (Harris *et al.*, 1997; Harris *et al.*, 1999) and we have previously distinguished between GD1 and GD3 by looking for absent or intermittently missed quick phases during OKN testing. However, the presence or absence of SIF only tells us whether or not there is neurological involvement. By assessing the main sequence of the OKN quick phases we will now have the opportunity to monitor not only the progression of the disease but also the effects of treatment.

We appreciate that GD is rare but, nevertheless, identification of eye movement abnormalities has aided in the management and possibly prolonged the life of some of our patients. GD, however, may not be the only condition in which early detection of slow saccades leads to earlier intervention and, as a result, improves or prolongs the life of a patient. Not only neurometabolic diseases have been found to be associated with slow saccades but in adults slow saccades have been reported in a number of conditions (see Table 4.3). The spectrum of diseases in infants and children differs from that in adults and examination of OKN quick phases will give us the opportunity to determine the full range of conditions associated with slow saccades in childhood. Examining the speeds of OKN quick phases would also be a simple test to distinguish between sixth nerve palsy and non-paralytic esotropia, which can sometimes be difficult to do in young patients. We would expect saccades to be slowed in the abducting eye in cases of sixth nerve palsy but to be of normal speeds in a non-paralytic esotropia.

As well as being too slow saccades can be too fast. Fast horizontal saccades are a rare clinical finding but have been reported in some patients with saccadic oscillations such as flutter and opsoclonus (Bergenius, 1986) and in some patients with stutters (Doslak *et al.*, 1986). Small-amplitude saccades that appear to be too fast occur when a saccade is interrupted in mid-flight. Thus, the saccade rather than being too fast is actually too small. These small-amplitude horizontal saccades are characteristic of myasthenia gravis (Oohira *et al.*, 1986; Barton *et al.*, 1995). Also abnormalities in the orbit, such as tumours, that restrict the motion of the eye can lead to these seemingly fast saccades. If OKN testing could be used to identify such conditions as infantile myasthenia gravis or obstructions of the globe, this would further indicate that it has a significant role to play in the assessment of infants and children.

8.1.2 Gaze position during horizontal OKN

In Chapter 5 we studied the position of gaze during full-field horizontal OKN testing. We noted, as have others, that during full-field horizontal OKN the mean position of gaze was shifted in the opposite direction to stimulus movement ("contraversion"). We found that this is a robust phenomenon occurring even at very low stimulus speeds. We also carried out a detailed study of a child with excessive contraversion. The child, who had a vestibulocerebellar disorder, on optokinetic stimulation immediately adopted an extreme contraversive deviation. This shift in gaze induced a gaze paretic nystagmus with slow phases in the same direction as the curtain rotation. The only explanation for contraversion proposed so far is that it enables perusal of the oncoming visual scene. We suggest that patients with vestibulocerebellar disorders, who have poor tracking ability, contravert to use their

'leaky' neural integrators in an attempt to match stimulus velocity. A similar strategy to enhance velocity-matching could explain contraversion in normal subjects.

The observation that vestibulocerebellar patients adopt an extreme contraversive deviation may indicate an additional clinical use of OKN testing. It is believed that the neural integrator has a brainstem and a cerebellar component. The brainstem integrator has a time constant of about 1.5s. The cerebellar component of the neural integrator is thought to be responsible for augmenting the time constant to its normal value of around 25s. The patient that we studied had a time constant of about 1-2s and on optokinetic stimulation immediately adopted an extreme contraversive deviation. Thus, we suggest that this extreme response could be an indication of dysfunction of the cerebellar component of neural integration.

Currently, neural integrator function may be quantitatively assessed by calculating a time constant. On fixation of an eccentrically placed target the elastic restoring forces of the orbit pull the eye back toward the central position with a time course that approximates a negative exponential. The rate of this centripetal drift of the eyes indicates the time constant of the neural integrator; 63% of the drift back to the midline is equivalent to one time constant. This measure of integrator function is impossible to perform in the young child. We suggest that examination of gaze position during horizontal OKN could be a simple way of quantitatively assessing the function of the neural integrator. Further studies relating neural integrator time constant values to measures of contraversion are required before we can use contraversion as a quantative measure of neural integrator function.

8.2 Vertical OKN

8.2.1 Vertical OKN quick phases

In Chapter 6, in order to determine if vertical OKN quick phases could be used as a substitute for measuring vertical saccades, we compared these eye movements in healthy adult subjects. We found that the main sequences for duration and the main sequences for peak velocity of vertical saccades and vertical OKN quick phases had similar shapes. However, vertical saccades were significantly faster (just) than vertical OKN quick phases. Therefore, it may not be appropriate to use the vertical OKN quick phase main sequence as a *precise* measure of the vertical saccadic main sequence. Nevertheless, since vertical saccades and vertical OKN quick phases have been found to be similarly affected by brainstem disease (Büttner-Ennever *et al.*, 1982; Hanson *et al.*, 1986), measuring vertical quick phase dynamics may well provide a means of identifying brainstem pathology when it is not possible to determine a saccadic main sequence. This requires further investigation but, since quick phases of larger amplitudes were rarely elicited during our vertical OKN testing, any comparisons would be limited to amplitudes less than 10°.

Electro-oculography and infrared limbal reflection are unreliable techniques for the measurement of vertical eye movements. The most reliable recording method is the magnetic search coil but unfortunately this method is not suitable for testing infants and children. However, in Chapter 7 we found that simply by the observation of eye movements, it was possible to detect an absence of upward and/or downward OKN quick phases. When there is a paucity of quick phases the eyes are seen to "lock-up" at the limit of gaze, where they remain unless a quick phase eventually occurs. Thus, identification of lock-up to an upward and/or downward moving

stimulus identifies VSIF. In the infants and children that we studied, VSIF was frequently associated with a neurometabolic disease or with a lesion involving the brainstem (particularly the rostral midbrain). We found that VSIF was not always associated with HSIF.

8.2.2 Vertical OKN slow phases

In Chapter 6 we assessed the slow phases of vertical OKN in healthy adult subjects. When compared to the slow phases of horizontal OKN, the vertical OKN slow phases had a lower gain. Also, the vertical response displayed more intersubject variability than the horizontal response. Other investigators have found that the slow phase velocity gain of upward OKN was greater than the slow phase velocity gain of downward OKN and we confirmed this. We suggest that, until further quantitative clinical studies have been conducted and as normal vertical OKN is variable, clinical significance should be attached to the finding only when the response is grossly asymmetric.

Little is known about vertical OKN in patients with visual system pathology. In Chapter 7 we identified, by observation of eye movements, abnormal vertical OKN. In addition to our findings concerning absent vertical OKN quick phases (see 8.2.1) we identified a number of children with a complete absence of upward and/or downward OKN. Absent vertical OKN was associated with lesions of the cortex, brainstem and/or cerebellum. Of particular importance was the finding that in some patients there were differences between horizontal and vertical OKN. We found that abnormal vertical OKN but normal horizontal OKN is suggestive of a rostral midbrain lesion. Our study demonstrates that vertical OKN testing *in addition* to horizontal OKN testing does indeed have a useful role in the detection of neurological

abnormalities in infants and children. However, further studies are needed to determine whether quantitative recording of eye movements during vertical OKN testing would have additional value. Also, it will be necessary to study systematically the development of vertical OKN in normal children.

An asymmetry in the monocular horizontal OKN response in human subjects, who have had normal visual development interrupted early in life, has been well documented. On the other hand, vertical OKN responses in such subjects have not been so well studied. Therefore, we studied the monocular and bi-ocular vertical optokinetic responses in patients with misalignment of their visual axes since childhood. In the majority of the patients and the control subjects we found a similar asymmetry of bi-ocularly and monocularly viewed vertical OKN, with upward OKN stimulus motion eliciting a higher gain. However, the vertical optokinetic responses in the patients were often significantly poorer than those recorded from control subjects and the patients' responses were very variable. Thus, it appears that individuals with disturbances of binocular vision from childhood, as well as showing abnormalities of horizontal OKN may show abnormalities of vertical OKN. However, from the small, heterogeneous group of patients that we studied it was not possible to clearly define these abnormalities or to determine what factors cause them. We suggest that, in patients with disorders of binocular vision, vertical optokinetic responses deserve further systematic study. It would also be interesting to compare patients with a specific anomaly (e.g. latent nystagmus, DVD or nasal-temporal asymmetry) to those without. Likewise, a comparison of the different ages of onset of binocular deprivation would be of interest.

8.3 Conclusions

The studies of this thesis demonstrate that OKN testing should be an integral part of the oculomotor assessment. We have shown that electro-oculography is sufficient for identifying abnormalities in the horizontal response and, simply by observation, gross abnormalities of the vertical response can be recognised. Although in the testing of the young child a full-field stimulus is ideal, a stimulus that is large enough so that the child is not distracted by what is around it, is probably sufficient. In departments with facilities to perform visual electrodiagnostic studies, it may actually be possible to carry out OKN testing in the same recording session and with only slight adaptations of the equipment.

By testing horizontal and vertical OKN we can make assumptions about the integrity of the cortex, cerebellum and brainstem. OKN testing prior to neuroimaging would direct the radiologist as to the area of the brain on which to concentrate. Further, as neuroimaging of infants and children requires sedation, which always carries a risk and indeed in very sick patients may be out of the question, OKN testing could provide a useful alternative in some cases. OKN testing also gives us the opportunity to monitor disease progression.

The main findings of this thesis that will have implications in our clinical work are: -

1) Examination of OKN quick phases can provide a simple means for approximating the saccadic main sequence and for identifying patients with brainstem abnormalities.
2) From at least 2 months of age, slow horizontal OKN quick phases and horizontal saccades should be considered as abnormal.

3) A shift in gaze position immediately on horizontal optokientic stimulation could be a clinical sign of cerebellar disease.
4) In addition to horizontal OKN, examination of vertical OKN can provide valuable information about the state of the patient's oculomotor system.
5) Absence of the slow or the quick phases of vertical OKN should indicate further investigations for a neurometabolic disease or an abnormality involving the cortex, brainstem, and/or cerebellum.
6) Abnormal vertical OKN with normal horizontal OKN is suggestive of a rostral midbrain lesion.

We conclude that OKN testing is currently undervalued as a clinical tool and that it does have an important role in the assessment of the oculomotor system both as a visual response and as a motor behaviour.

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Appendix – Supporting Publications and Presentations

Garbutt, S., Harwood, M.R., and Harris, C.M. (2002)
Anticompensatory eye position ("contraversion") in optokinetic nystagmus.
Annals of the New York Academy of Sciences. **956:** 445-448.

Garbutt, S., Harwood, M.R, and Harris, C.M. (2001)
Comparison of the temporal characteristics of reflexive saccades and the quick phases of optokinetic nystagmus (OKN).
British Journal of Ophthalmology. **85:** 1477-1483.

Garbutt, S., Cassidy, L., Kriss, A., Nischal, K.K., and Harris, C.M. (2000)
Absent horizontal and vertical optokinetic nystagmus in infants and children.
Presented at the *Annual Congress of Ophthalmologists, Harrogate, UK.*

Garbutt, S., and Harris, C.M. (2000)
Abnormal vertical optokinetic nystagmus in infants and children.
British Journal of Ophthalmology. **84:** 451-455.

Garbutt, S., Harwood, M.R., and Harris, C.M. (2000)
The temporal main sequence of optokinetic nystagmus.
[ARVO abstract]. Investigative Ophthalmology and Visual Science. **41**(4): 701.

Garbutt, S., and Harris, C.M. (1999)
Detection of vertical saccade initiation failure using an OKN projection system.
In Transactions of the IXth International Orthoptic Congress, Stockholm, Sweden.
Pritchard, C., Kohler, M., and Verlohr, D. (eds.) pp. 95-98.

Garbutt, S., and Harris, C.M. (1999)
Abnormal vertical optokinetic nystagmus – Preliminary findings.
Presentation at the *Child Vision Research Society Meeting, London, UK.*

Anticompensatory Eye Position ("Contraversion") in Optokinetic Nystagmus

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KEYWORDS: **optokinetic nystagmus; anticompensatory eye movement; gaze position; beating field; cerebellum**

INTRODUCTION

The quick phases of full-field optokinetic nystagmus (OKN) not only reset the eyes, but also move them in an anticompensatory direction (that is, in the opposite direction to stimulus movement, "contraversion").[1–7] Although recognized as an oculomotor phenomenon, contraversion is poorly understood, and it has been suggested as a strategy for directing the line of sight into the visual field from which motion is originating.[5–7] We have previously observed extreme contraversion in patients with absent smooth pursuit and a leaky eye position integrator.[8] In this study we examined contraversion in healthy adults and propose a model for this behaviour based on observation from a clinical group.

METHODS

OKN was recorded from 10 healthy adults and an affected child from a family with a dominant vestibulocerebellar disorder.[8] Horizontal eye movements were measured using an infrared limbus eye tracker and bi-temporal dc-electro-oculography simultaneously. OKN was elicited by rotation of a full-field patterned curtain rightward and leftward at speeds of 2–30 deg/s, in steps of 2 deg/s. The direction and speed of the stimulus was randomized. Subjects were instructed to keep the curtain as clear as possible, but not to track any individual feature. Each step of optokinetic stimulation lasted 20 seconds followed by a 10-second fixation period.

The mean gaze position during stimulus motion was determined for each stimulus speed and direction. This was calculated from the start and end of each quick phase and then subtracted from the steady-state eye position prior to stimulus onset.

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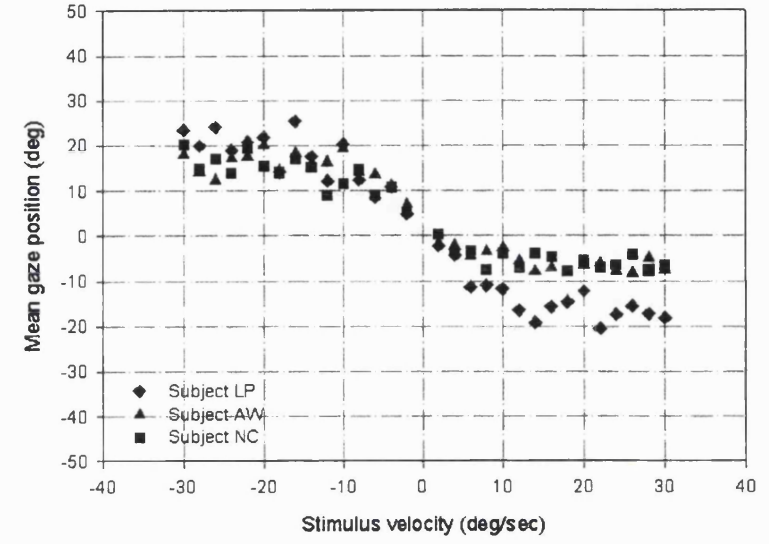

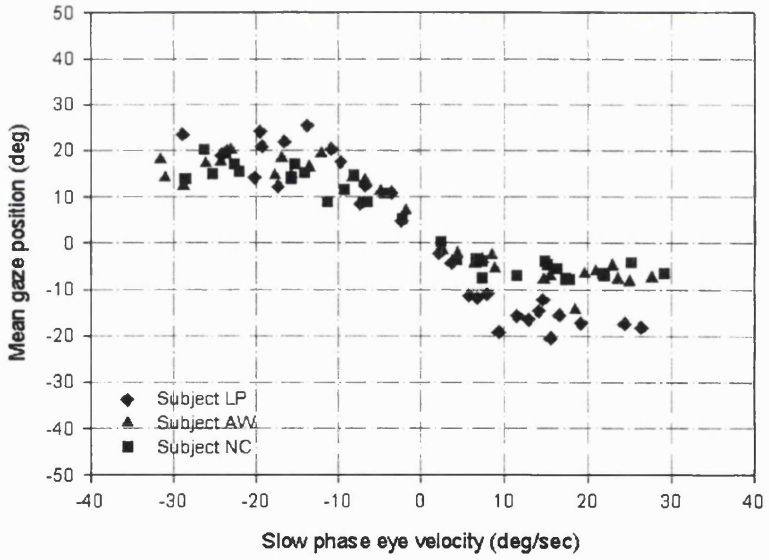

FIGURE 1, A and B. Representative responses in three normal subjects. (**A**) Mean gaze position plotted against stimulus velocity. (**B**) Mean gaze position plotted against slow phase eye velocity.

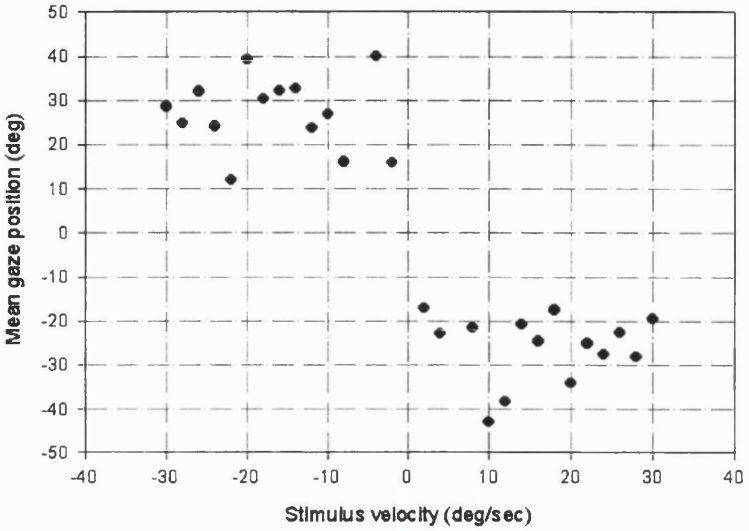

FIGURE 1C. Response from the child with a vestibular-cerebellar disorder. Mean gaze position plotted against stimulus velocity.

RESULTS

The mean gaze always shifted in the direction of the quick phase even at very low stimulus speeds. After onset of stimulus motion, usually two or more OKN quick phases were required to drive the subject's eyes away from the primary position into a new mean position of gaze. In normal subjects contraversion was *not* all-or-none, but showed a gradual increase with stimulus velocity up to about 10–15 deg/s, and saturated for higher velocities (FIG. 1A). In the normal subjects the mean saturated position shift was 12.5 degrees (FIGS. 1A and B). The vestibulocerebellar patient had poor smooth pursuit and on OKN stimulation immediately adopted a contraversive deviation of on average 24.5 degrees (FIG. 1C).

DISCUSSION

In normal subjects contraversion is not an all-or-none phenomenon, but increases with stimulus velocity up to about 10–15 deg/s before saturating. In patients with very poor/absent smooth pursuit (i.e., no fast OKN response) and a very leaky integrator, contraversion is a rapid all-or-none response. Thus, the stimulus for contraversion cannot be slow-phase eye velocity, but may be an internal reconstruction of stimulus velocity (e.g., efference copy) or retinal slip. We propose that the extreme contraversion seen in vestibulocerebellar patients reflects a "vestigial" system to match stimulus velocity with the subjects' own gaze-evoked nystagmus slow phases

(pseudo-OKN) (rather than an optokinetic response seen in normals). A similar strategy to enhance velocity-matching could explain the less dramatic and graded contraversion in normal subjects, as velocity matching would be enhanced by even a slightly imperfect integrator. Thus, contraversion matches velocity when precise positioning is not needed or impossible. According to this hypothesis, contraversion, smooth pursuit (fast OKN) and the neural integrator are manifestations of the same function, namely, matching velocity and position as demanded by the visual apparatus or task.

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ORIGINAL ARTICLES—Laboratory science

Comparison of the main sequence of reflexive saccades and the quick phases of optokinetic nystagmus

Siobhan Garbutt, Mark R Harwood, Christopher M Harris

Abstract

***Background/aims*—Abnormalities in the saccadic main sequence are an important finding and may indicate pathology of the ocular motor periphery or central neurological disorders. In young or uncooperative patients it can be difficult eliciting a sufficient number of saccades to measure the main sequence. It is often assumed that the quick phases of optokinetic nystagmus (OKN) are identical to saccades. If this were the case, it would be feasible to use OKN, an involuntary response that is easily evoked, as a simple way of eliciting many saccades. The aim of this study was to determine whether reflexive saccades and the quick phases of OKN are indeed identical, and whether OKN quick phases could have a clinical role in identifying patients with slow saccades.**

***Methods*—OKN and reflexive saccades were recorded from 10 healthy adults using an infrared limbus eye tracker and bitemporal DC electro-oculography simultaneously. OKN was stimulated by rotating a full field patterned curtain around the subject at 10–50°/s. Reflexive saccades were elicited to red LED targets at 5–20° eccentricity.**

***Results*—OKN quick phases tended to have a longer duration compared to saccades, but these differences were not significant. OKN quick phases had a slightly lower peak velocity compared to saccades, which was statistically significant ($p<0.05$).**

***Conclusion*—The main sequence for duration is the same for reflexive saccades and OKN quick phases. The main sequence for peak velocity is slightly faster for reflexive saccades than OKN quick phases, but the difference is unlikely to be of clinical significance. As an illustration of the potential of this technique, the authors demonstrate that OKN quick phases show similar slowness to saccades in a child with brainstem pathology caused by Gaucher disease type III. It is concluded that recording OKN may be a simple clinical means for approximating the main sequence.**

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Both the duration and peak velocity of saccades can be characterised by their stereotypical relation with respect to saccade amplitude. This relation is known as the main sequence.[1 2] For saccades above about 4°, duration increases linearly with amplitude. Linearity is lost at the larger amplitude end of the spectrum around 50°. Peak velocity also increases with amplitude but there is a progressive saturation beyond amplitudes of 20°, with asymptotic values of about 500°/s.[3] Unlike the relation between duration and amplitude, that between peak velocity and amplitude is non-linear.

It is impossible to voluntarily alter the velocity of a saccade[4–6] and thus significant slowing is regarded as a pathological sign.[3] Slow saccades with a restriction of ocular motility usually reflect abnormalities in the ocular motor periphery, such as ocular muscle or ocular motor nerve paresis, or lesions of the medial longitudinal fasciculus. Conjugate slow saccades in patients with a full ocular range are usually caused by central neurological disorders.[3] To identify patients with slow saccades it is preferable to record their main sequences for duration and peak velocity,[7] and therefore it is necessary to elicit a large number of saccades over a range of amplitudes. This can be difficult to achieve in infants and uncooperative patients, or in patients who already have difficulty in triggering saccades. Indeed, in children with saccade initiation failure (SIF) ("ocular motor apraxia"), it is crucial to detect any slowing of saccades, as this can distinguish progressive neurological disease from the more benign classic congenital SIF (Cogan's apraxia).[8] In this study we investigated the possibility of measuring the speed of quick phases of optokinetic nystagmus (OKN) as a substitute for measuring saccade speed, as OKN is an involuntary behaviour that can be easily evoked from most patients, even in infancy.

Clinical and neurophysiological studies have indicated that horizontal saccades and the quick phases of vestibular and optokinetic nystagmus (OKN) have the same anatomical substrate in the paramedian pontine reticular formation (PPRF).[9–13] Therefore, a priori, it seems plausible that saccades and quick phases should have similar speeds, and that a disease

process causing a slowing of saccades should also lead to slowing of quick phases. A number of investigators have compared the main sequences for duration and/or peak velocity of saccades and quick phases of optokinetic or vestibular nystagmus (VN) showing some degree of similarity, but some inconsistencies have also been reported. Thus, in monkeys and cats it has been shown that spontaneous saccades and the quick phases of vestibular nystagmus, induced by rotation, share the same temporal characteristics.[14 15] In humans, some studies have concluded that voluntary saccades, elicited to fixed targets in the light, are similar to OKN quick phases.[16–19] In contrast, Henriksson *et al*[20] and Gavilán and Gavilán[21] found some significant differences between these rapid eye movements. Both groups of investigators found that saccades had a significantly higher velocity (peak velocity measured by Henriksson *et al*; average velocity measured by Gavilán and Gavilán) than OKN quick phases. These discrepancies may reflect methodological differences. Some investigators have measured only duration, others only velocity (peak velocity or average velocity), and some both. Also different studies have compared the fast phases of nystagmus with voluntary saccades elicited under different condition (light and/or dark; eyes open/eyes closed). Further, different recording techniques (electro-oculography; infrared reflection) and signal processing may have produced different results.

In this study we re-examine this issue with the ultimate aim of being able to routinely measure the main sequence from OKN quick phases for clinical use. Here, we compare the peak velocity and duration main sequences of reflexive saccades with OKN quick phases in normal adult subjects in the light. We also compare two eye movement recording techniques used simultaneously, infrared limbal reflection (IR) and DC electro-oculography (EOG). IR was chosen because it is very accurate; however, it is cumbersome and of limited value in the paediatric clinical setting. In our paediatric eye movement laboratory we routinely use EOG, which is clinically practical for patients of all ages but not as accurate as IR. Before we could consider applying this technique for recording the main sequence in infants and children we felt that it was necessary to determine that both recording methods yielded similar results. Further, as discussed above, in the literature some investigators have reached opposing conclusions regarding whether saccades and quick phases are the same in humans. These discrepancies could be explained by the choice of recording technique. By using both infrared tracking and electro-oculography we controlled for this variable.

Finally, in the discussion we will illustrate the measurement of the main sequence with OKN from a child diagnosed with neuronopathic Gaucher disease (type III), a condition characterised by severe SIF and slow saccades.[8]

Methods

Ten healthy adult subjects aged between 25 and 48 years (mean 28.4 years) were recorded. None had a history of strabismus or any known neurological or ocular motor problems. Horizontal eye movements were measured using an infrared limbus eye tracker (Iris, Skalar Medical, Delft, Netherlands) and bitemporal DC electro-oculography (EOG) simultaneously. The infrared limbus eye tracker (IR) had a horizontal linear range of plus or minus 25° with an accuracy of 3 min arc. For the EOG recording, self adhesive silver/silver chloride electrodes were placed at the outer canthus of each eye, and a common mode reference electrode was sited at the mid-forehead. Subjects' heads were supported in a chin rest and the importance of keeping their heads still was stressed. Alertness was maintained by frequent verbal encouragement. Subjects were randomly assigned as to whether they had horizontal OKN or reflexive horizontal saccades tested first.

A full field, brightly coloured, patterned curtain was used as the horizontal optokinetic stimulus.[22] This was rotated around the subject for a total time of 5 minutes. The curtain was rotated rightward and leftward at speeds of 10, 20, 30, 40 and 50°/s, for periods of 30 seconds each. The direction and speed of the stimulus was randomised. Subjects were instructed to look straight ahead and keep the curtain as clear as possible, but not to track any individual feature.

The stimulus for eliciting reflexive saccades consisted of red LEDs mounted on a black horizontal stimulus arc. Saccades of 5, 7.5, 10, 15, and 20° eccentricity, to the left and right were elicited. The order of target eccentricity was randomised and a total of 40 target illuminations (20 to the left and 20 to the right) were presented at each eccentricity, in a pseudo random order. As the peripheral target was illuminated the central target was extinguished simultaneously. Only centrifugal saccades were analysed.

Eye movements recorded using IR and EOG were digitised and sampled at 1090 Hz, then stored on digital audio tape. These eye position data were filtered using a zero phase low pass digital filter (3 dB point = 64 Hz), and differentiated to give an estimate of eye velocity. A saccade or OKN quick phase (fast eye movement (FEM)) was detected when the velocity was continuously above 100°/s for at least five points. The high threshold was chosen to avoid accidental detection of slow phases and to eliminate small corrective FEMs that we were not interested in. The peak velocity of each FEM was determined. FEM onset and offset were then defined as the last points either side of the peak velocity before which the velocity fell below 10°/s. On account of the higher level of associated instrument noise, the EOG data were refiltered (3 dB point = 30 Hz) before applying the above onset/offset detection algorithm. These points were used to calculate the amplitude and duration of the FEMs. Only FEMs with an amplitude >4°

were used for regression and statistical analysis, and eye movements to the right were examined independently from those to the left. All eye movements associated with blinks were rejected.

To quantifiably compare saccade and quick phase dynamics, for each subject regressions were fitted to the duration and peak velocity main sequences for saccades and for OKN quick phases (Fig 1), and the slope and intercept values were used for statistical purposes. The relation between peak velocity and amplitude is not a linear one (Fig 1B) and therefore a logarithmic (base 10) plot (Fig 1C) was constructed for each subject, before performing linear regressions. This process is equivalent to a power law fit.

Statistical analysis was unaffected by choice of logged or unlogged slope and intercepts. For clarity, unlogged values are shown throughout the paper.

The slope and intercept values of the linear regressions are co-dependent; higher regression slopes are associated with lower regression intercepts. Thus, in order to determine if there were statistical differences between saccades and OKN quick phases, it was necessary to use a multivariate analysis of variance (MANOVA), taking the slope and intercept as the independent variables. Statistical significance is assumed at a p=0.05 level throughout.

Results

Our saccadic data lie within previously reported ranges. For the saccadic duration-amplitude main sequences recorded by IR we report individual values for the slope that ranged from 1.51 to 3.10 ms/deg (mean 2.10 ms/deg) and an intercept that ranged between 20.15 and 31.35 ms (see Table 1). In the literature reported individual values for the slope range from 1.5 to 3 ms/deg (with means clustered between 2 and 2.7 ms/deg) and intercept values typically range from 20 to 30 ms.[5 7 23 24] Also the main sequence relation that we found between saccade peak velocity and amplitude is quite typical of that which has been reported previously.[1 25 26] Our OKN measures were also similar to those reported in the literature,[27 28] with a typical decrease in slow phase velocity gain (from values up to 0.87) with increasing optokinetic stimulus velocity.

COMPARISON OF FEMS RECORDED USING THE INFRARED LIMBUS EYE TRACKER

The duration of saccades and OKN quick phases differed slightly, but were not statistically different (see Table 1, Fig 2A). For a given amplitude, OKN quick phases tended to have a longer duration compared with saccades.

There were also differences in the peak velocity of saccades and OKN quick phases (see Table 1, Fig 2B). Statistical testing demonstrated that unlike for duration these differences *were* significant. For a given amplitude, OKN quick phases tended to have a lower peak velocity compared to saccades. There were some idiosyncratic differences between eye movements to the right and those to the left. However, these differences were not statistically significant.

COMPARISON OF FEMS RECORDED USING ELECTRO-OCULOGRAPHY

As with the data recorded by IR, the differences in the duration-amplitude main sequences of saccades and quick phases were not significantly different. Similarly, as with the peak velocities recorded using IR, the differences between the peak velocity-amplitude main sequences of

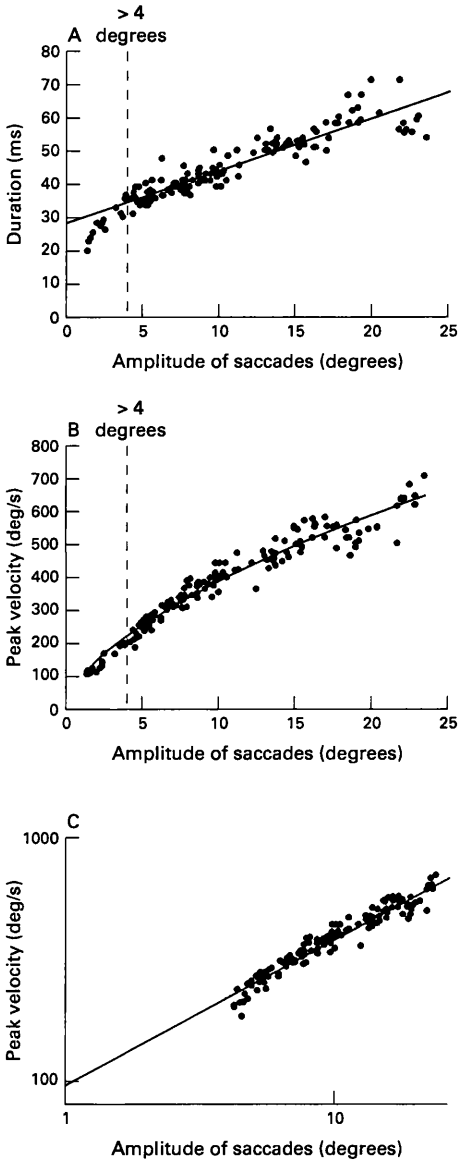

Figure 1 Typical saccadic main sequences for duration and peak velocity. These plots were derived from saccades recorded from subject 6 using infrared limbal reflection. (A) Scatter plot for saccadic duration versus saccadic amplitude. Linear regression line for saccadic amplitudes >4° also shown. (B) Plot demonstrating the non-linear relation between saccadic peak velocity (PV) and saccadic amplitude (A). Curve fitted according to $PV = I.S^{\log A}$, where I and S are unlogged values of the linear regression intercept and slope for log PV versus log A. (C) Logarithmic plot of PV versus A, for saccadic amplitudes >4°. Linear regression line also shown.

Table 1 Main sequence parameters recorded using infrared limbal reflection

	Duration-amplitude relation								*Peak velocity-amplitude relation*							
	Saccades				*OKN quick phases*				*Saccades*				*OKN quick phases*			
	Right		*Left*		*Right*		*Left*		*Right*		*Left*		*Right*		*Left*	
Subject	*S ms/°*	*I ms*	*S ms/°*	*I ms*	*S ms/°*	*I ms*	*S ms/°*	*I ms*	*S*	*I*	*S*	*I*	*S*	*I*	*S*	*I*
1	1.54	30.79	1.55	31.35	1.68	30.82	1.97	30.82	4.57	87.10	4.47	87.10	4.57	72.44	5.62	57.54
2	3.10	22.33	2.18	25.79	2.87	28.31	2.34	27.65	2.19	144.54	3.24	112.20	3.47	81.28	4.68	72.44
3	1.81	23.43	2.04	26.04	1.62	26.47	1.89	28.21	3.98	97.72	3.72	93.33	4.17	89.13	4.90	70.79
4	2.31	28.76	2.02	30.41	2.36	30.81	3.02	29.36	3.72	87.10	3.47	97.72	5.01	60.26	5.33	58.88
5	1.97	27.25	1.77	24.06	2.54	24.10	2.73	20.79	3.63	89.13	3.47	114.82	3.63	87.10	2.88	120.23
6	1.94	25.95	1.51	28.52	1.62	29.90	1.65	27.09	3.89	97.72	4.27	93.33	6.17	60.26	4.90	79.43
7	1.73	27.18	2.04	24.30	1.64	26.21	1.49	28.86	3.02	125.89	3.47	109.65	5.01	72.44	5.37	67.61
8	2.22	21.97	2.13	20.82	1.88	23.47	2.21	20.97	2.51	141.25	2.88	141.25	3.02	114.82	3.34	120.23
9	3.03	20.15	1.94	29.67	3.18	21.72	2.23	27.75	2.82	109.65	3.39	102.33	3.24	87.10	4.17	77.62
10	2.62	25.34	2.43	22.56	2.71	22.19	1.96	22.61	2.69	117.49	3.72	97.72	2.95	102.33	3.89	97.72
Mean	2.23	25.32	1.96	26.35	2.21	26.40	2.15	26.41	3.30	109.76	3.61	104.95	4.12	82.72	4.51	82.25

The slope (S) and intercept (I) values for the duration-amplitude (D-A) relation were obtained from a linear regression of the main sequence for duration for amplitudes >4°. The slope and intercept values for the peak velocity-amplitude (PV-A) relation were obtained from a linear regression of the logged main sequence for peak velocity for amplitudes >4°, such that $PV = I.S^{loeA}$ (see Methods and Fig 1B, C).

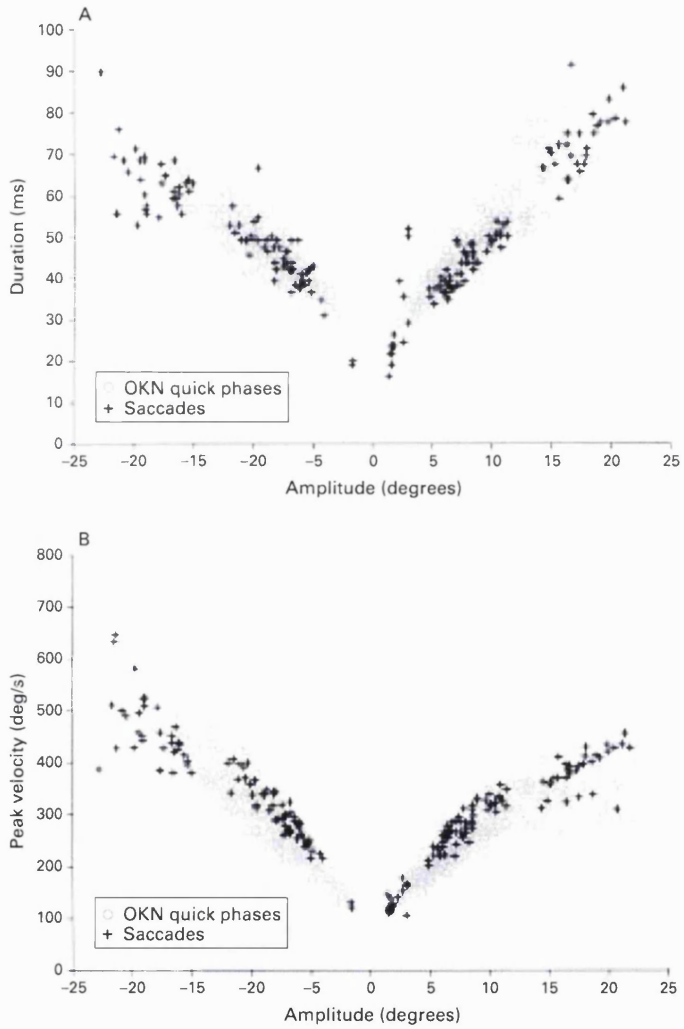

Figure 2 Scatter plot of the saccadic and OKN quick phase main sequences for duration (A) and for peak velocity (B) for a typical subject (subject 9). Data recorded using infrared limbal reflection.

saccades and quick phases recorded by EOG were significantly different (Table 2).

The main sequence parameters for duration and peak velocity recorded using EOG were compared to those recorded using IR. No statistical differences were found. The similarities are illustrated by comparing confidence regions for each recording device (Fig 3). The ellipses represent 95% confidence bounds on the probability that the population mean slope *and* intercept lie within and are centred on the group means (see Tables 1 and 2). Greater intersubject variability is reflected in larger confidence regions.

Discussion

Statistical analysis demonstrated that the saccadic main sequence for duration was not significantly different from the OKN quick phase main sequence for duration. In animals it has been demonstrated that the duration-amplitude main sequence for spontaneous saccades is the same as that for VN quick phases.[14 15] It has also been shown that both spontaneous saccades and the quick phases of VN are similarly affected by light and darkness. Three studies have compared the duration-amplitude main sequences of saccades and OKN quick phases in humans,[16 19 29] and concluded that they were similar. Mackensen and Schumacher[16] tested only two subjects, but concluded that the duration-amplitude main sequences of these FEMs were the same. They also noted that the intrasubject differences were quite marked and that there were differences between FEMs made to the right compared to the left. We also noted large intrasubject differences and for individual subjects there were also directional differences. Jürgens *et al*[19 29] compared optokinetic quick phases to voluntary saccades. They found that the duration-amplitude main sequences for these two FEMs scattered around the same regression line. Our results support their findings and suggest that measurement of the OKN quick phases duration-amplitude main sequence in infants or uncooperative patients could be used clinically to assess the functioning of the saccade system.

We found that OKN quick phases tended to have a lower peak velocity compared to reflexive saccades. The fact that we found differences between the peak velocities of these FEMs but no differences in the duration may imply that

Table 2 Main sequence parameters recorded using electro-oculography

	Duration-amplitude relation								*Peak velocity-amplitude relation*							
	Saccades				*OKN quick phases*				*Saccades*				*OKN quick phases*			
	Right		*Left*		*Right*		*Left*		*Right*		*Left*		*Right*		*Left*	
Subject	*S ms/°*	*I ms*	*S ms/°*	*I ms*	*S ms/°*	*I ms*	*S ms/°*	*I ms*	*S*	*I*	*S*	*I*	*S*	*I*	*S*	*I*
1	1.50	28.00	1.71	27.19	1.68	30.72	1.78	29.42	4.47	89.13	4.27	95.50	4.47	64.57	5.62	63.10
2	2.57	19.43	2.46	23.08	3.22	19.63	3.43	19.95	2.04	138.04	3.02	114.82	3.16	79.86	4.07	75.86
3	2.27	16.44	2.33	16.24	2.97	17.83	2.83	18.34	3.89	104.71	3.72	97.72	4.27	91.20	4.47	79.43
4	2.18	27.12	2.39	27.80	2.69	28.35	3.25	26.07	3.63	85.11	3.63	91.20	4.47	64.57	4.90	56.23
5	1.71	27.19	1.63	26.85	2.39	26.32	2.48	28.87	4.27	79.43	3.16	102.33	3.72	74.13	3.16	102.33
6	1.92	25.34	1.58	28.60	1.63	26.85	2.13	23.43	3.72	91.20	3.98	97.72	5.62	53.70	5.37	70.79
7	1.96	26.97	2.05	26.47	1.97	25.80	2.42	27.20	3.09	128.82	3.24	117.49	4.57	79.43	5.01	68.79
8	1.85	21.67	1.78	18.38	2.17	19.00	2.10	15.71	2.57	141.25	2.69	131.83	3.02	117.49	3.02	120.50
9	2.86	18.50	2.35	26.01	3.34	21.15	3.26	18.61	2.51	117.49	3.09	107.15	2.82	91.20	3.24	79.43
10	2.30	19.11	2.44	18.59	2.43	19.51	2.53	19.73	2.24	134.90	2.88	114.82	2.57	97.72	3.72	91.20
Mean	2.11	22.98	2.07	23.92	2.45	23.52	2.62	22.73	3.24	111.01	3.37	107.06	3.87	81.39	4.26	80.77

The slope (S) and intercept (I) values for the duration-amplitude (D-A) relation were obtained from a linear regression of the main sequence for duration for amplitudes >4°. The slope and intercept values for the peak velocity-amplitude (PV-A) relation were obtained from a linear regression of the logged main sequence for peak velocity for amplitudes >4°, such that $PV = I.S^{log A}$ (see Methods and Fig 1B, C).

reflexive saccades and OKN quick phases have slightly different shaped trajectories (this is currently under investigation). In the literature OKN quick phases in humans have variously been reported to have a lower peak velocity than saccades,[20] lower peak velocity at greater amplitudes (>20°) than saccades,[17] or indistinguishable from saccades.[16–19 29] The different conclusions reached may be partly explained by exactly what type of saccade was used for comparison. The peak velocity of saccades differs depending on the type of saccade elicited (in the light or dark, reflexive or voluntary). Indeed, it is believed that the neural mechanisms generating reflexive and voluntary saccades are at least partially different,[30] and this could result in them having different dynamics. Erkelens and Hulleman[30] attempted to determine the neural mechanisms controlling reflexive and voluntary saccades by looking at the effects of lesions. They concluded that voluntary saccades are most probably generated via the frontal eye field

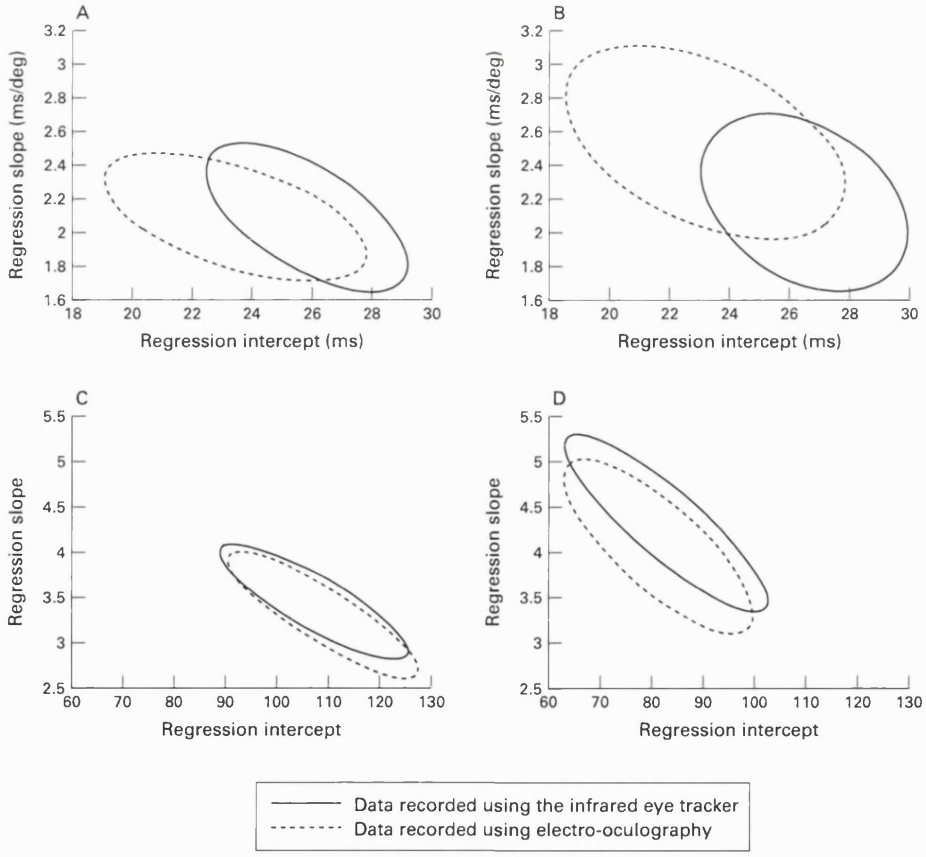

Figure 3 Illustration of bivariate confidence regions comparing results recorded using infrared limbal reflection, and those recorded using electro-oculography. Ellipses show 95% confidence regions for the population slope and intercept of the duration (A, B) and peak velocity (C, D) main sequence parameters. (A, C) Saccades. (B, D) OKN quick phases.

pathways, whereas collicular pathways seem to be more important in the control of reflexive saccades. Also the peak velocities of saccades differ depending on the direction of the saccade. For example, it is well documented that centripetal saccades have faster kinematics than centrifugal saccades.[26 31–35] In our experiment we compared reflexive centrifugal saccades with OKN quick phases. We chose to do this because quick phases are essentially centrifugal movements since they not only reset the eyes but also move the eyes in an anticompensatory direction (that is, in the opposite direction to stimulus movement, "contraversion").[36] A further consideration is the fact that in humans the OKN response differs depending on the attentional state of the subject. Depending on the instructions given by the investigators, subjects can assume different attitudes towards an optokinetic stimulus. Ter Braak[37] distinguished between "look-OKN" and "stare-OKN." Stare-OKN is obtained by instructing the subject to look passively at the stimulus, without any deliberate attempt to pay attention to specific features. Stare-OKN has a low gain, low amplitude, and frequent quick phases.[38] In contrast, look-OKN is elicited by instructing the subject to track single details in the moving stimulus. The OKN exhibited has a high gain, large amplitude slow phases, and infrequent quick phases.[38] Becker[39] suggested that the quick phases of look-OKN could conceivably resemble goal directed saccades, whereas the quick phases of stare-OKN, which do not profit from the selection of identified visual targets, may be slower. We attempted to elicit stare-OKN by instructing our subjects to look straight ahead and keep the curtain as clear as possible but to not track any individual target. Therefore, Becker's argument may explain why we found that the peak velocities of reflexive saccades were higher than the quick phases of OKN. However, we did not really know the mental set of the subjects and the OKN elicited was most probably a mix of look-OKN and stare-OKN.

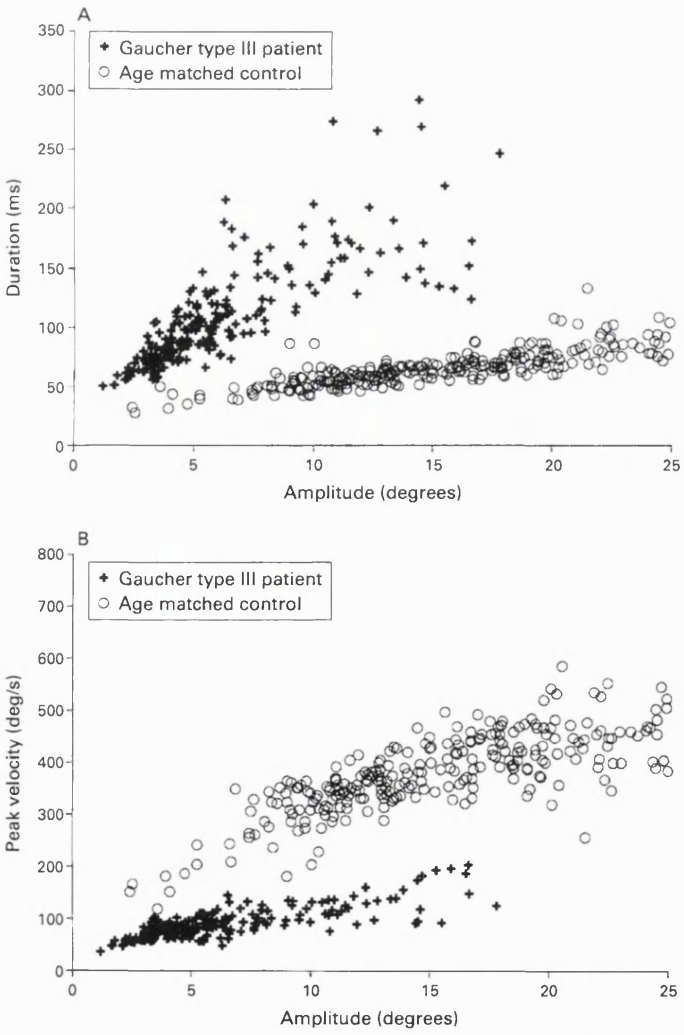

Figure 4 The OKN main sequences for duration (A) and peak velocity (B) of a patient with Gaucher disease type III and an age matched control.

Another consideration is the range of amplitudes that are compared. Henriksson *et al*[20] found that the differences between the peak velocities of saccades and OKN quick phases were more pronounced at greater amplitudes. Dichgans *et al*[17] found that the differences between the peak velocities of saccades and OKN quick phases were statistically significant only at amplitudes greater than 20° (and only to the left). This may explain why investigators who compared only a limited range of amplitudes (Mackensen and Schumacher[16] 0–20°; Sharpe *et al*[18] 0–10°) found no differences in the peak velocities of saccades and OKN quick phases. We limited comparisons to amplitudes between 4–25°, because of the restrictions in the linear range of the IR eye tracker.

The peak velocity differences that we found are slight enough that it seems unnecessary to hypothesise separate neural circuits for the generation of these two types of rapid eye movements. The small differences may only indicate that rapid eye movements are initiated in the same neural circuits but in slightly different ways.

The duration values we obtained using EOG were in good agreement with those recorded using IR, although scatter was greater, owing to the increased noise inherent in the EOG measurement technique. Bahill *et al*[40] established their normative database of saccadic durations using IR. Compared with other laboratories where EOG had been used, Bahill and co-workers' data coincided reasonably well (see Becker[39]). On the other hand, Baloh *et al*[7] using EOG, reported much larger values for saccadic durations. However, this is probably not because they used EOG, but was more likely the result of their signal processing.

We also found that the peak velocity main sequence parameters for saccades and OKN quick phases were similar whether recorded using IR or by EOG. In the literature saccadic peak velocities recorded using IR[2 25] are comparable with EOG studies.[7 39] Clearly different from most other work is the normative database of Bahill *et al*,[40] with its extremely

large peak velocities. However, these differences are unlikely to be attributable to the use of IR reflection, but rather because they eliminated any saccades that were noticeably slower than optimum, as conceivably affected by "fatigue." Our results, together with those discussed above, confirm that, in the clinical setting, it is suitable to use EOG to measure the duration and peak velocity of saccades and OKN quick phases.

To illustrate the usefulness of this technique we examined a child with Gaucher disease type III (GD III) and a child that was age matched. Where it has been possible to assess horizontal saccades in children with GD III they have been reported as slow.[8] It is very important to recognise slow saccades in these patients since in the presence of otherwise normal ocular motility and range, slow saccades in association with saccade initiation failure (seen in all GD III patients) indicates severe brainstem disease. We recorded eye movements using bitemporal EOG and used the same protocol for eliciting OKN as above. The data were analysed in the same way, although the threshold for peak velocity was reduced to 10°/s. In the child with GD III, OKN quick phases had a longer duration and lower peak velocity compared with the age matched control (Fig 4). Statistical analysis demonstrated that the differences in the OKN quick phases between the patient and control were highly significant. Additional clinical studies are needed; however, this finding suggests that measuring OKN quick phases may be a simple means for approximating the main sequence and thus a useful clinical tool for identifying brainstem pathology. Furthermore, OKN is an involuntary response that is easily elicited and thus the greatest use of this technique would be in young or uncooperative patients in whom it would be impossible to determine a saccadic main sequence. Also, the simplicity of OKN testing would permit serial recordings giving objective measurement of disease progression. Currently it is not known which conditions are associated with slow saccades in infants and children; however, this technique gives us the opportunity to examine this.

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ABSENT OPTOKINETIC NYSTAGMUS IN VISUALLY UNRESPONSIVE INFANTS.

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Introduction: It has previously been shown that testing optokinetic nystagmus (OKN) has a useful role in the assessment of the visually unresponsive infant as it can be used to identify cases of delayed visual maturation (DVM) and saccade initiation failure (SIF) 'ocular motor apraxia'. In DVM a response to a full-field horizontally moving stimulus viewed with both eyes open can be elicited and in SIF OKN quick phases are intermittently absent and the eyes intermittently 'lock-up' in the direction of stimulus movement. However, a complete absence of response to a horizontally and a vertically moving optokinetic stimulus in the visually unresponsive infants has not previously been investigated.

Methods: Horizontal OKN (HOKN) was tested by rotating a patterned curtain around the infant. Vertical OKN (VOKN) was tested by projecting vertically moving horizontal black and white stripes onto a large, back-projected viewing screen. HOKN and VOKN were tested with both eyes open. HOKN was recorded by electroculography and simultaneous video recording. VOKN eye movements were not recorded objectively, but a video recording was made of the infant's eye movements throughout testing.

Results: Over the period of one year 31 infants were referred for eye movement assessment because they were clinically visually unresponsive. 11 of these infants had no response to a horizontally or vertically moving optokinetic stimulus. 10 of the infants with a complete absence of OKN underwent a MRI scan, and in 9 a cortical abnormality was identified. In the majority this abnormality was extensive.

Conclusion: Absent HOKN and VOKN in the visually unresponsive infant is highly suggestive of an extensive cortical abnormality.

ORIGINAL ARTICLES—Clinical science

Abnormal vertical optokinetic nystagmus in infants and children

Siobhan Garbutt, Christopher M Harris

Abstract

***Aims*—To determine if testing vertical optokinetic nystagmus (VOKN) has a role in the clinical assessment of infants and children.**

***Methods*—A large field projection system was developed with which optokinetic nystagmus (OKN) could be stimulated in any direction. Gross abnormalities in the response were detected simply by observation.**

***Results*—VOKN was tested in 144 children using this OKN projection system. 26 of these children had abnormal VOKN; 13 had a vertical saccade initiation failure "ocular motor apraxia" (in either direction, up/down, or in both) and 13 had absent VOKN (in either direction, up/down, or in both). Nine of the children with an up and/or down vertical saccade initiation failure (VSIF) had a neurometabolic disease (two had Niemann–Pick disease type C, five had Gaucher disease type III, one had Gaucher disease type II, and one had Gaucher disease type I). Five children with a VSIF had an abnormality identified by a magnetic resonance imaging (MRI) scan of the brain. In two of these children there was a focal lesion of the rostral midbrain. In 11 of the children with absent up and/or down VOKN an MRI scan revealed an abnormality. This involved the brainstem and/or the cerebellum in 10. Absent up and/or down VOKN was found in association with Joubert syndrome, Leigh disease, and cerebral palsy.**

***Conclusion*—VOKN testing has a useful role in detecting neurological abnormalities in infants and children. Detection of abnormal VOKN should indicate further investigations for a neurometabolic disease or an abnormality involving the cortex, brainstem, and/or cerebellum. Abnormal VOKN but normal horizontal OKN is highly suggestive of a rostral midbrain lesion.**

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Optokinetic nystagmus (OKN) is a reflexive oscillation of the eyes induced by motion of the whole or, at least, a very large part of the visual field. The OKN response consists of an alternating sequence of following movements (slow phases) and fast resetting saccades (quick phases). OKN can be elicited even from the newborn[1 2] and if the whole visual field moves it is virtually impossible to suppress.

Horizontal OKN (HOKN) has been studied extensively. Among its many roles in the clinical assessment of infants and children, testing HOKN is useful in identifying lesions that affect the horizontal optokinetic pathway (involving the cortex, brainstem, or cerebellum). A unilateral lesion of this pathway will result in poorer HOKN to the same side as the lesion.[3] A complete absence of HOKN can indicate a bilateral lesion affecting the horizontal optokinetic neural pathway. HOKN testing is also useful in the identification of horizontal saccade initiation failure (HSIF) or "ocular motor apraxia". Traditionally, HSIF has been identified by recognition of head thrusting and/or synkinetic blinking. However, as these compensatory behaviours are not always adopted, identification of absent HOKN quick phases is considered to be a more reliable test for HSIF.[4]

The neural pathways controlling vertical OKN (VOKN) have not been clearly established, therefore abnormalities in the vertical optokinetic response are not as well understood as abnormal HOKN. However, if we consider the quick phase of VOKN to be a vertical saccade and the slow phase to be a vertical smooth pursuit movement, we can go some way towards explaining the neural control of VOKN. The frontal eye fields and superior colliculi are responsible for the generation of vertical (and horizontal) saccades.[5] From here the pathways controlling vertical saccades have not been fully elucidated, but it is believed that before reaching the vertical ocular motor nuclei they are relayed via the rostral interstitial nuclei of the medial longitudinal fasciculus (riMLFs). This pair of nuclei in the rostral midbrain contain vertical saccade burst neurons,[6–8] and thus are crucial for the generation of vertical saccades. The pathways responsible for vertical smooth pursuit most likely originate in the posterior hemisphere.[5] Again the pathways to the vertical ocular motor nuclei are not fully understood. In the monkey, at least, the dorsolateral pontine nuclei (DLPN) are considered to be a crucial relay since following unilateral DLPN lesions vertical and horizontal smooth pursuit are

impaired.[9] It is thought that the flocculus of the cerebellum is likely to be involved since bilateral flocculectomy results in major abnormalities in the slow phases of VOKN and HOKN.[10] Additionally, it is known that neurons that discharge in relation to vertical pursuit can be found in the dentate nucleus and in the Y-group of the vestibular nuclei,[11 12] and some vertical pursuit signals are also found in the medial longitudinal fasciculus (MLF).[13 14] The final supranuclear relay in the midbrain reticular formation has not been identified, but the interstitial nucleus of Cajal is considered to play an important part in the control of vertical smooth pursuit.[15] Thus, we can infer that the neural pathways controlling VOKN most likely involve the cortex, brainstem (particularly the rostral midbrain), and cerebellum, and presumably abnormalities of these areas could result in abnormal VOKN.

HOKN may be effectively elicited by rotating a patterned curtain around a stationary subject. VOKN, on the other hand, is more difficult to stimulate and record effectively, and this is probably the reason why it has not been as thoroughly investigated as HOKN. To determine if VOKN has a useful role in the clinical assessment of infants and children we developed a projection system with which we could stimulate OKN in any direction.

Methods

OKN was elicited by back projecting a black and white grating on to a large viewing screen. This screen was 165 cm wide and 120 cm high. The children sat in a hydraulic chair facing the screen, their eyes level with its centre, at a distance of 60 cm (Fig 1). Older children sat alone, younger children sat on a parent's lap. The head was immobilised by a headrest or was held by the parent or the examiner.

Horizontal black and white stripes moved vertically to elicit VOKN and vertical stripes moved horizontally to elicit HOKN. The stimulus covered approximately 108 degrees of the horizontal visual field and 90 degrees of the vertical visual field. The grating had a spatial frequency of 0.04 cycles/degree and moved at a velocity of 28 degrees/second. Lighting was at a low ambient level.

Horizontal and vertical OKN were tested in each child and OKN was recorded as present, absent, or lock up. Lock up identified cases of saccade initiation failure (SIF). In SIF the quick phases of OKN are intermittently missed and so the unchecked slow phase drives the eyes to the mechanical limit of gaze where they remain "locked up" until a quick phase eventually occurs.

Figure 1 View of the OKN projection screen.

As part of a standard eye movement protocol, VOKN was tested in 144 children referred to the eye movement laboratory at Great Ormond Street Hospital. These children were referred from ophthalmology, metabolic, and neurology departments over a period of 1 year. Reasons for referral included unusual eye movements, unusual head movements, visual unresponsiveness, or suspicion of a neurometabolic disease.

Results

In 118 of the 144 children tested, a response to an upward and a downward moving optokinetic stimulus was observed with no evidence of lock up. These children were considered to have "normal" VOKN, although their eye movements were not recorded objectively and therefore any subtle differences in the response elicited by an upward moving stimulus compared with that elicited by a downward moving stimulus would not have been detected. The remaining 26 children had obviously abnormal VOKN. Of these, 13 had a vertical SIF (VSIF) (in either direction, up/down, or in both) and 13 had absent VOKN (in either direction, up/down, or in both). There were 12 males and 14 females.

Nine of the children with a VSIF had a neurometabolic disease (two had Niemann–Pick disease type C, five had Gaucher disease type III, one had Gaucher disease type II, and one had Gaucher disease type I). Five children with a VSIF had an abnormality identified by a magnetic resonance imaging (MRI) scan of the brain.

In 11 of the children with absent up and/or down VOKN an MRI scan revealed an abnormality. This involved the brainstem and/or the cerebellum in 10. These results are summarised in Table 1.

All 26 of the children with abnormal VOKN had vertical and horizontal ocular movements on the doll's head manoeuvre. In all the children with a VSIF vertical smooth pursuit appeared normal, and saccades in the direction opposite to lock up could only be elicited by the use of a head thrust or by blinking synkinetically, if at all. In those with a complete absence of OKN, no smooth pursuit could be elicited in any direction. In those with an absence of up VOKN, smooth pursuit was absent upwards but present downwards. The reverse was true for those with absent down VOKN. Vertical saccades were not formally tested because we have found these very difficult to elicit reliably even in normal children. All children had pupils that were equal and reactive to light apart from one child (patient 1) who had a dilated right pupil that did not react to light.

Table 1 Summary of patients with abnormal vertical optokinetic nystagmus

	Sex	Age	U	D	L	R	MRI results/diagnosis
1	M	10y7m	Lu	+	+	+	MRI, midline abnormality of the midbrain, periaqueductal grey matter, symmetrical abnormality of dorsal pons. Symmetry of the lesions favours a metabolic disorder
2	F	7y6m	Lu	Lu	+	+	MRI, bilateral occipital infarcts, right frontoparietal lesion. Haemorrhagic ischaemic infarct following mild birth asphyxia
3	M	7y9m	Lu	Lu	+	+	Niemann–Pick disease type C
4	F	14y	Lu	Lu	+	+	Niemann–Pick disease type C
5	F	8y5m	Lu	Lu	+	+	Gaucher disease type I. MRI, haemorrhagic lesion in the rostral midbrain of unknown aetiology
6	F	0y9m	Lu	Lu	Lu	Lu	Gaucher disease type II
7	F	5y5m	Lu	Lu	Lu	Lu	Gaucher disease type III
8	F	10y9m	Lu	+	Lu	Lu	Gaucher disease type III
9	F	4y7m	Lu	+	Lu	Lu	Gaucher disease type III
10	F	3y10m	Lu	+	Lu	Lu	Gaucher disease type III
11	F	4y1m	+	Lu	Lu	Lu	Gaucher disease type III
12	M	4y9m	+	Lu	Lu	Lu	MRI, dysmorphic basal ganglia, small corpus callosum, underdeveloped brainstem, particularly the pons
13	F	2y5m	Lu	Lu	–	–	MRI, generalised decrease in bulk of the brain and delay in maturation of myelin
14	F	5y11m	+	–	+	+	MRI, abnormality in right cerebellar white matter, right cerebellar peduncles and the right medulla. Appearances consistent with acute inflammatory or neoplastic lesion
15	F	2y	–	+	+	+	MRI, dilatation of the whole ventricular system, as a result of hydrocephalus
16	M	3y	–	+	+	+	MRI, lesion within the medial thalamic nuclei. Aetiology not known, possibly a metabolic disorder or post-viral encephalitic damage
17	F	8y9m	+	–	+	+	MRI, bilateral symmetrical abnormality in upper part of the cerebral peduncles extending into the lower parts of the thalami on both sides. Leigh disease
18	M	2y2m	–	–	Lu	–	MRI, discrete white matter lesions, lesions in basal ganglia and abnormality in the thalamus on both sides. Aetiology not known, possibly because of atypical infection
19	M	1y7m	–	–	Lu	+	MRI, incomplete cerebellar and dorsal pontine myelination, marked maturational delay
20	M	1y	+	–	Lu	–	MRI, cerebellar vermis hypoplasia, increased prominence of superior cerebellar peduncles. Joubert syndrome
21	M	2y6m	–	–	–	–	MRI, absent cerebellar vermis, arachnoid cyst in the left posterior fossa. Joubert syndrome
22	M	6y2m	–	–	–	–	MRI, multiple cerebral infarcts, due to antenatal thrombosis of aorta. Cortical blindness
23	M	5y5m	–	–	–	–	MRI, white matter changes adjacent to posterior aspect of lateral ventricles, abnormality at cerebellar pontine angle. Appearances consistent with degeneration/demyelination
24	M	4y10m	–	–	–	–	MRI, lesion in the brainstem near the IIIrd nerve nucleus. Focal ischaemia most likely aetiology
25	M	16y7m	–	–	–	–	Cerebral palsy. No MRI
26	F	1y7m	–	–	–	–	Undiagnosed neurodevelopmental disorder. MRI, no abnormality

y = years, m = months, U = response to an upward moving optokinetic stimulus, D = response to a downward moving optokinetic stimulus, L = response to a leftward moving optokinetic stimulus, R = response to a rightward moving optokinetic stimulus, + = OKN present, – = OKN absent, Lu = lock up.
The first 13 patients listed are those with a vertical saccade initiation failure (in either direction, up/down, or both). The final 13 patients listed had absent VOKN (in either direction, up/down or both).
NB Lock up in response to an upward moving stimulus indicates a saccade initiation failure of down saccades. Lock up in response to a downward moving stimulus indicates a saccade initiation failure of up saccades.

Discussion

We first consider those children with a VSIF—that is, absence of upward and/or downward quick phases and thus lock up on VOKN testing, and discuss the most relevant cases. As mentioned above, the riMLFs, part of the midbrain reticular formation, are believed to be crucial for the generation of vertical saccades and presumably optokinetic quick phases. Experimental lesions and clinicopathological studies suggest that from the midbrain reticular formation, the efferent fibres for vertical saccades/optokinetic quick phases and those for vertical smooth pursuit travel together to the vertical oculomotor nuclei.[7 16] All the children described in this study with a VSIF had normal vertical smooth pursuit, therefore, their VSIF is most likely to be the result of a lesion of the riMLFs themselves or afferent fibres to them. This is consistent with an abnormality of the midbrain, periaqueductal grey matter, and dorsal pons identified in one child (patient 1) and with an underdevelopment of the brainstem, particularly the pons, in another (patient 12).

One child (patient 2) was found to have a lesion involving the right frontoparietal region. This could account for the VSIF as it may have affected the frontal eye fields. However, since the frontal eye fields, along with the superior colliculi, are responsible for generating both vertical and horizontal saccades,[5] we would expect a HSIF to also be evident. This was not the case. It is more likely, therefore, that there was a lesion in the area of the rostral midbrain. Unfortunately, neuroimaging of this area was inconclusive.

Acquired VSIF has been documented in certain neurometabolic diseases, such as Niemann–Pick disease type C, Gaucher disease type II and III, Tay–Sachs disease and Wilson disease.[17–23] SIF in neurometabolic disease indicates dysfunction of supranuclear ocular motor control. Nine of the children identified with VSIF in this study had a neurometabolic disease. This relatively large number of children with a neurometabolic disease and a VSIF reflected the pattern of patients referred to our laboratory. In this study, two children (patients 3 and 4) with a VSIF were diagnosed as having Niemann–Pick disease type C. Deficits in the generation of rapid vertical eye movements are frequently seen in cases of Niemann–Pick type C[17 18] and indeed a VSIF may be the presenting sign of the disease,[23] as was the case with one child (patient 4) reported here. Neville and co-workers[18] described the typical sequence of ocular motor abnormalities seen in Niemann–Pick disease. This begins with loss of vertical saccades and absence of OKN quick phases (particularly affecting down gaze), followed by impairment of vertical smooth pursuit and then similar involvement of horizontal movements with reduced velocity of saccades to voluntary and optokinetic stimuli. Finally convergence is affected. The two patients reported in this study were presumably in the early stages of disease, since only their vertical saccades and optokinetic quick phases (both up and down) were affected. Vertical

smooth pursuit, horizontal saccades, HOKN, and convergence were all intact.

The ocular motor abnormalities in neuronopathic Gaucher disease have been outlined recently[24] and these include HSIF, strabismus, slow horizontal and downward saccades, and an abnormal vestibulo-ocular reflex. HSIF is the most consistent finding and is frequently the first sign of neurological involvement. Thus, identification of this in patients with Gaucher disease is crucial for their diagnosis and management as it indicates that they have the neuronopathic form of the disease—that is, type II or III. In our experience, when there is dysfunction of supranuclear ocular motor control in Gaucher disease, horizontal gaze is always affected first and thereafter involvement of vertical eye movements may indicate progression of the disease. Therefore we were surprised to find that in one child (patient 5) there was only an SIF in the vertical plane, with normal HOKN. However, an MRI scan revealed a lesion in the rostral midbrain with the appearance of an old haemorrhage. This presumably was the cause of the VSIF. Thus, despite the identification of an SIF her current diagnosis is of Gaucher disease type I (that is, the non-neuronopathic form), although she is still under investigation.

Of the 13 cases of VSIF identified in this study, seven had an HSIF. HSIF has been associated with a wide range of conditions[25] but is frequently found to be idiopathic. Of the 13 cases of VSIF identified in this study none was idiopathic. Thus, the presence of a VSIF, whether associated with a HSIF or not, should always indicate investigations for a more sinister cause. Equally, identification of HSIF should lead to testing of the vertical plane.

A VSIF will not necessarily involve both upward and downward saccades and as we have seen here saccades in only one direction may be affected. It has been suggested that saccades may be lost in only one vertical direction because burst neurons for upward and downward saccades are topographically arranged within the riMLFs. Büttner-Ennever and colleagues[7] suggested that the medial aspect of the riMLFs contain neurons involved in upgaze while neurons from the lateral portion are primarily involved in downgaze. Thus, it is plausible that a more medially situated lesion would result in a VSIF affecting only upward saccades and a laterally placed lesion a VSIF of downward saccades, while a more extensive lesion would lead to a complete VSIF. This view is controversial, however, and others[16] have reached opposite conclusions regarding the arrangement of vertical burst neurons within the riMLFs. In neurometabolic diseases it appears that downward saccades are often affected before upward saccades. This has been observed in Niemann–Pick disease[18] and in Gaucher disease.[24] This preferential loss of downward saccades was also evident in the children with Gaucher disease type III in this study.

Next we consider those 13 children with absent VOKN—that is, those with no response to an upward and/or downward moving optokinetic stimulus. As discussed above the VOKN neural pathways most likely involve the cortex, brainstem, and cerebellum. In one child (patient 22) with a complete absence of VOKN there was cortical involvement. In six of the children with absent up and/or down VOKN an abnormality that specifically involved the cerebellum and/or brainstem was identified by MRI scan. One child (patient 14) was reported to have an abnormality of the right medulla and cerebellum, a second (patient 19) had incomplete cerebellar and dorsal pontine myelination, and a third (patient 23) had an abnormality at the cerebellar pontine angle. A lesion in the brainstem near the third nerve nucleus was identified in one child (patient 24). The third nerve nucleus lies partly within the MLF and thus complete absence of OKN, along with an internuclear ophthalmoplegia and a partial third nerve palsy, are consistent findings. Two cases (patients 20 and 21) with abnormal VOKN had a diagnosis of Joubert syndrome. Ocular motor abnormalities have previously been reported in association with Joubert syndrome,[26 27] and it is believed that they are secondary to dysfunction of both the cerebellum and the brainstem.[27]

Four children with absent up and/or down VOKN had a lesion that most probably involved the rostral midbrain. The first child (patient 15) had hydrocephalus and dilatation of the whole ventricular system; dilatation of the third ventricle could affect the rostral midbrain. Three children (patients 16,17, and 18) had lesions that involved the thalamus. Although there have been reports of thalamic lesions affecting vertical gaze[28–31] there is no anatomical documentation for thalamic control of vertical gaze. Therefore, it is more probable in these three cases that there was a disruption of the pathways controlling vertical gaze in the adjacent rostral midbrain.

In this study nine children (patient numbers 1, 2, 3, 4, 5, 14, 15, 16, and 17) had abnormal VOKN but normal HOKN. Of these nine children, six (patient numbers 1, 2, 5, 15, 16, and 17) had a lesion that most probably specifically involved the rostral midbrain. Thus, it appears that abnormal VOKN but normal HOKN is highly suggestive of a rostral midbrain lesion.

Since we found that VOKN may only be absent in one direction, there clearly is some segregation between the neural pathways for up VOKN and those for down VOKN. However, it is not known to what extent these pathways are separate. Although the VOKN pathways have not been fully elucidated it has been proposed[16] that the tracts involved in upgaze decussate through the posterior commissure, while those for downgaze do not pass through the commissure and possibly decussate near the oculomotor nuclei. However, from the results of MRI scans alone it is not possible for us to reach any conclusions regarding the exact organisation of these pathways.

Conclusion

VOKN testing has a useful role in detecting neurological abnormalities in infants and children. The OKN projection system is an effective clinical tool for testing VOKN. By simple observation, lock up, and thus cases of VSIF, can be identified as can absent VOKN. However, further investigations are required to determine if objective recording of eye movements during VOKN testing would have additional value.

In this study, VSIF was frequently associated with a neurometabolic disease. VSIF was also associated with lesions involving the brainstem, patricularly the rostral midbrain. Absent VOKN was associated with lesions of the cortex, brainstem and/or cerebellum. Abnormal VOKN but normal HOKN is highly suggestive of a rostral midbrain lesion.

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THE TEMPORAL MAIN SEQUENCE OF OPTOKINETIC NYSTAGMUS.

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Purpose: Abnormalities in the temporal main sequence of saccades can indicate brainstem pathology. In sick children, however, it is often not possible to elicit sufficient saccades to calculate a main sequence. It has previously been shown that the amplitude-duration and the amplitude-peak velocity characteristics of saccades and optokinetic nystagmus (OKN) quick phases are similar. Thus in the uncooperative patient it may be feasible to use OKN, a reflexive response that is easily elicited, to calculate the amplitude-duration and the amplitude-peak velocity main sequence. The aim of this study was to determine if this was possible in healthy adult subjects before applying it to infants and children in the clinical setting. **Methods:** OKN and reflexive saccades were recorded from 6 healthy adults. OKN was elicited by rotating a full-field patterned curtain around each subject at 10 to 50 deg/s. Saccades were elicited to red LED targets at 5 to 20 degrees eccentricity. Eye movements were recorded using an infrared eye-tracker. **Results:** Linear regression of the amplitude-duration main sequence parameters and of the logged amplitude-peak velocity parameters indicated that there were differences between OKN quick phases and saccades. The OKN quick phases tended to have a longer duration (OKN mean intercept=28.6ms, slope=1.8ms/deg; saccadic mean intercept=26.5ms, slope=1.9ms/deg) and a lower peak velocity (OKN mean intercept=86.7deg/s, slope=4.4s^{-1}; saccadic mean intercept=118.3deg/s, slope=3.2s^{-1}). Bivariate 95% confidence regions demonstrated that for the amplitude-duration parameters these differences were not statistically significant. However the differences in the amplitude-peak velocity parameters were statistically significant. **Conclusion:** The reason for these differences in the peak velocity and subtle differences in the duration of OKN quick phases and saccades is not yet known. Nevertheless these findings suggests that OKN could be used to determine an amplitude-duration main sequence that is comparable to an amplitude-duration main sequence for saccades. This is potentially a useful clinical tool in detecting brainstem abnormalities in uncooperative and very young patients.

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DETECTION OF VERTICAL SACCADE INITIATION FAILURE USING AN OKN PROJECTION SYSTEM

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INTRODUCTION

Saccade initiation failure (SIF) ("ocular motor apraxia") is a term used to describe an intermittent inability to initiate saccades. This includes an intermittent delay or failure in the triggering of quick phases during optokinetic nystagmus (OKN) and vestibular nystagmus. SIF can occur in the horizontal or the vertical plane and it may be congenital or acquired. Although hoizontal SIF is frequently found to be idiopathic, it has been associated with a wide range of conditions.[1] Vertical SIF (VSIF) is unusual and generally indicates a lesion of the rostral interstitial nucleus of the medial longitudinal fasciculus (riMLF) in the rostral midbrain[2] or afferent fibres to it, or a neurometabolic diseases, such as Niemann-Pick type C[3,4] (in which it may be the presenting sign[5]) or Gaucher disease (types II and III).[6,7] Thus, VSIF is an important clinical sign.

Head thrusting to shift gaze is a manoeuvre adopted by many children to compensate for their saccade deficit. The detection of head thrusting has traditionally been used for the identification of cases of SIF. However, it may not always be adopted[8,9,10] and in older children it may be superseded by a strategy in which triggering of saccades is facilitated by blinking at the same time as the saccade (synkinetic blinking).[11] Normal children and adults may also blink synkinetically and thus recognition of synkinetic blinking does not always help in the diagnosis of SIF. Instead of looking for these compensatory behaviours, a more reliable test for SIF is to examine the quick phases of induced OKN. When quick phases are intermittently missed during OKN testing, the slow-phases will drive the eyes to the mechanical limit of gaze, where they stay 'locked-up' until a quick phase eventually occurs.[8,12]

Here we will discuss a method for identifying vertical lock-up and thus VSIF using an OKN projection system.

METHOD

Vertical OKN was reflexively elicited by projecting vertically moving black and white stripes onto a large-field, back-projected viewing screen. Testing was carried out with both eyes open. A video recording was made of the patients throughout testing.

VSIF was identified as episodes of absent OKN quick phases, when the eyes were seen to 'lock-up' in extreme vertical deviation in the direction of grating movement.

RESULTS

Using this experimental set-up we examined a number of patients at Great Ormond Street Hospital and initially identified 5 who demonstrated episodes of lock-up during vertical OKN testing. All of these patients had normal vertical ocular movements on the doll's head manoeuvre and normal vertical pursuit.

In all 5 cases identification of VSIF proved to be crucial for their diagnoses. On examination of the MRI scans, an abnormality was identified in 2 of the patients. The 3 other patients were subsequently found to have a neurometabolic disease; 1 had Gaucher Type III and 2 had Niemann-Pick Type C.

Since writing the abstract for this paper we have identified a further 9 patients with VSIF.

Patient	Up OKN	Down OKN	Diagnosis
RD	Lock-up	Lock-up	GD III
LA	Lock-up	Lock-up	N-P C
JR	Lock-up	Lock-up	N-P C
DM	Lock-up	Absent	Incomplete myelination of DP and cerebellum
JG	Lock-up	Normal	Midline abnormality of MB, peri-aquaductal gray matter and symmetrical abnormality of DP
NV	Lock-up	Lock-up	Normal MRI scan, presumed N-P C*
SG	Lock-up	Lock-up	Delayed maturation of myelin
GB-S	Lock-up	Lock-up	Frontal parietal lesion, infarcts of occipital lobes**
IG	Lock-up	Absent	Undiagnosed neurodevelopment disorder***
K K-R	Lock-up	Normal	Normal MRI scan, presumed N-P C*
MC	Lock-up	Normal	GD III
SS	Lock-up	Normal	GD III
NF	Poor	Lock-up	GD III
PW	Poor	Lock-up	Dysmorphic BG, small CC, underdeveloped BS

Table 1. Patients in the study. Up OKN = response to upward moving OKN stimulus, Down OKN = response to downward moving OKN stimulus, GDIII = Gaucher Disease Type III, N-P C = Niemann-Pick Type C, DP = dorsal pons, MB = midbrain, BG = basal ganglia, CC = corpus callosum, BS = brainstem.

*Awaiting fibroblast culture results from Lyon, France to confirm diagnosis.
**Imaging of rostral midbrain inconclusive.
***MRI not possible due to low grade fever.

DISCUSSION

The frontal eye fields and superior colliculi are responsible for generating vertical saccades as well as horizontal ones.[13] The precise pathways controlling vertical saccades have not been fully elucidated, but are thought to relay to the paired riMLF,

which contain vertical saccade burst neurons,[14-18] before reaching the vertical oculomotor nuclei. It is believed that efferent fibres for vertical pursuit and saccades travel together from the midbrain reticular formation to the vertical oculomotor nuclei.[17,19] Thus, abnormal vertical saccades but *normal* pursuit may be the result of a lesion of the riMLF itself or a lesion involving afferent fibres to it. This is consistent with the abnormality of the periaqueductal gray matter and/or the dorsal pons seen in two of our patients (JG, DM) and with the underdeveloped brainstem found in one patient (PW).

VSIF in neurometabolic diseases indicates dysfunction of supranuclear ocular motor control, and thus is a sign of neuronopathic disease. This again could indicate midbrain involvement and indeed this is consistent with postmortem reports. In one patient with Niemann-Pick disease postmortem showed widespread involvement of the brainstem alongside diffuse changes of the whole brain[20] and in Gaucher Disease Type III paramedial brainstem involvement has been reported at postmortem.[21]

A VSIF will not necessarily involve both upward and downward saccades and as we have seen here saccades in only one direction may be affected. It has been suggested[17] that the medial aspect of the riMLF contains neurons involved in upgaze while neurons from the lateral portion are primarily involved in downgaze. Thus, it is plausible that a more medially situated lesion would result in a VSIF affecting only upward saccades and a laterally placed lesion a VSIF of downward saccades, while a more extensive lesion would lead to a complete VSIF. This view is controversial however, and others[19] have reached opposite conclusions regarding the arrangement of vertical burst neurons within the riMLF.

CONCLUSION

Use of the OKN projection system to demonstrate lock-up during vertical OKN testing is a valuable tool in the identification of VSIF. A presentation of VSIF should indicate further investigations for neurometabolic disease and midbrain lesions.

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ABNORMAL VERTICAL OPTOKINETIC NYSTAGMUS - PRELIMINARY FINDINGS.

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Introduction : Optokinetic nystagmus (OKN) is a reflexive oscillation of the eyes induced by the motion of the whole or, at least, a very large part of the visual field. When the whole visual field moves it is virtually impossible to suppress OKN and as it can be elicited even from the new-born, it has a potentially important role to play in the clinical assessment of infants and children. Horizontal OKN (HOKN) has been extensively studied and may be effectively elicited by rotating a patterned curtain around a stationary subject. Vertical OKN (VOKN), on the other hand, is more difficult to stimulate and abnormalities of VOKN are not as well understood as abnormal HOKN.
VOKN has previously been stimulated using a hand-held black and white striped drum . This method, however, is far from perfect as only a small part of the visual field is stimulated and the velocity of the stimulus is not controlled. We have developed a projection system with which we can stimulate OKN in any direction. The purpose of this report was to determine the effectiveness of this system as a clinical tool for the identification of abnormal VOKN.

Methods: VOKN was reflexively elicited by projecting vertically moving horizontal black and white stripes onto a large, back-projected viewing screen. Testing was carried out with both eyes open. A video recording was made of the patients' eye movements throughout testing.

Results: Using this experimental set-up we identified a number of patients with abnormal VOKN; either absent VOKN in either direction (up or down) or both, or a vertical saccade initiation failure ('ocular motor apraxia'), again this may be in either direction or both. Vertical saccade initiation failure was identified as episodes of absent OKN quick phases when the eyes were seen to 'lock-up' in extreme vertical deviation in the direction of stimulus movement.
On further investigation of these patients with abnormal VOKN a significant number were found to have either a midbrain lesion or a neurometabolic disease (Gaucher disease Type III or Niemann-Pick disease Type C)

Conclusion: The OKN projection system is an effective clinical tool for the identification of abnormal VOKN. These are, however, preliminary results and further investigation of this method is required.
Abnormal VOKN should indicate further investigation for neurometabolic disease and midbrain lesions.

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