Vertical Optokinetic Nystagmus in Adults with or without Parkinson's Disease

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by

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1. General Introduction

1.1 An overview of the different types of eye movement

Eye movements are the result of a complex interaction of the six extra-ocular muscles of both eyes and enable the eyes to track and fixate on objects of interest in the visual field. They are under the control of three cranial nerve nuclei and their associated nerves, the 3rd (oculomotor) nerve, 4th (trochlear) nerve and 6th (abducens) nerve. Under physiological conditions, eye movements are a combination of a number of different types of voluntary and involuntary movements. These movements include smooth pursuit, saccades, vestibulo-ocular reflex, optokinetic nystagmus, vergence and fixational eye movements. They can also be sub-classified as fast and slow eye movements [1]. Fast eye movements are those with a peak linear velocity of 100°/s to 600°/s and include saccadic movements and optokinetic nystagmus (quick recovery phase), whereas slow eye movements have much lower velocities of between 5°/s and 50°/s. They include smooth pursuit, optokinetic nystagmus (slow tracking phase), vestibulo-ocular reflex, ocular following responses and vergence movements (convergence / divergence).

1.1.1 Smooth Pursuit

Smooth pursuit eye movements are slow movements enabling the eyes to follow an object across a visual field as well as allowing the eyes to maintain fixation on stationary objects in space.

The neurological control mechanisms of smooth pursuit are poorly understood, however anatomically the ascending pathways of the smooth pursuit system can be divided in to two major functional divisions. One involves the direct stimulation of retinal ganglion cells by moving stimuli. The fibres subsequently project to area 4Cα of the primary visual (striate) cortex (V1) via the magnocellular layers of the lateral geniculate nucleus (LGN). The second division responds to feature analysis, with fibres passing via the parvocellular layers of the LGN to area 4Cβ of the striate cortex (V1) [2 3]. The human homologue of the middle temporal visual area (MT) and medial superior temporal visual area (MST) which are predominantly concerned with the magnocellular routes, and the striate cortex play a major role in processing this information and generating smooth

pursuit eye movements. Other areas implicated in the generation of smooth pursuit include the frontal eye field, the cerebellum, the accessory optic system (AOS) of the midbrain and the nucleus of the optic tract (NOT) lying in the brachium of the superior colliculus [2 3]. The AOS projects indirectly to the dorsal cap of the inferior olive, and the interstitial nucleus of Cajal, and directly to the vestibular nuclei and the cerebellum [2]. Inputs come from the retina and project to the pontine nuclei, the magnocellular layers of the LGN, the thalamic nuclei and the inferior olive. The NOT is thought to encode for errors in retinal position, velocity and acceleration [3 4]. Lesions of the NOT result in impaired smooth pursuit [3 4].

1.1.2 Saccades

Saccadic movements are rapid conjugate movements, which quickly bring objects of interest in the visual field on to the fovea. They can be induced voluntarily as visually and non-visually guided movements [5]. Non-visually generated saccades can be initiated from memory, as can anti-saccadic movements, a movement equal and opposite in magnitude to a stimulating saccadic target [6].

The underlying neurological control mechanisms of volitional (memory guided) saccades involve the frontal eye field, supplementary eye field (learned sequences) and dorsolateral prefrontal cortex of the contralateral frontal lobe, with input from the basal ganglia (involved in target selection by acting as a gate) and the superior colliculus (communicates with saccade generators in the brainstem) [1 7]. Reflex saccades, which are visually driven, are responsible for re-orientating gaze on to new targets in space and are mediated by the superior colliculus with input from the parietal lobes. Bilateral stimulation of the frontal eye field in the frontal cortex appears to be responsible for vertical saccades [1 3].

Both volitional and reflex saccades are initiated by burst cells in the rostral interstitial nucleus of the medial longitudinal fasciculus of the midbrain (vertical saccades) and the paramedian pontine reticular formation (horizontal saccades) [1 3].

1.1.3 Vestibulo-Ocular Reflex

The vestibulo-ocular reflex is a reflexive movement, which allows integration of both head and eye movements. It is not dependant on visual stimulation, but is associated with balance and head movement.

All head movements stimulate the ampullae in the semi-circular canals of the inner ear and proprioceptors in the neck, with the subsequent information relayed to the vestibular nuclei. This in turn communicates with the oculomotor nuclei and results in compensatory eye movements to stabilise vision [1].

1.1.4 Ocular Following Response

Ocular following responses are brief movements initiated by a sudden unexpected stimulus movement in the visual field [8] and appear to help to stabilize gaze as well as generate version eye movements in response to planar motion [9]. They are initiated by the change in luminance associated with movement of the target stimulus and have minimum latencies in the order of 70-75 ms [8].

Animal studies suggest that the MT and MST are involved in the generation of the ocular following response [9].

1.1.5 Vergence

Vergence eye movements are disjugate movements that allow both eyes to maintain fixation on an object in space as its distance changes relative to an observer. Control centres are thought to be found in the parieto-occipital area and vergence centres in the midbrain [1].

1.1.6 Optokinetic Nystagmus

Optokinetic nystagmus is a reflexive movement that enable the eyes to track an object in a visual field. It is a slow tracking eye movement (slow phase) followed by a rapid resetting eye movement / saccade (quick phase) [1 10].

Vertical and horizontal optokinetic nystagmus are discussed further in this thesis, whilst there is very little in the literature concerning torsional OKN, although it appears that there is no clockwise or anticlockwise OKN asymmetry in normal healthy adults [11].

1.2 Motion Processing

The perception of motion is complex and whilst foveal motion sensitivity is assumed to be isotropic, that is, it is equal for movement in all directions, eccentric stimulation is anisotropic with a preference for centripetal motion [12]. Several models exist to try to explain the underlying neurological processes involved [13-16]. One of the most recent models suggest that directionally selective mechanisms exist to detect motion at high stimulus velocities, whist non-directional mechanisms operate at low velocities in both adults and infants [17]. These systems develop between the first 6 weeks and 5 months of life [18-20]. Those systems concerned with the processing of rapid movement appear to develop earlier than those concerned with slower velocities. Studies using motion visual evoked potentials (VEP) to assess motion perception in children support these theories since, no motion VEP asymmetry is seen in neonates, whereas by the age of 2-3 months a nasal asymmetry has developed. Interestingly the asymmetry disappears by the age of 6-8 months [21]. Re-organization of the binocular pathways therefore appears to occur in the post-natal period [22] .

Motion and visual preference can also be assessed in infants using forced preferential looking techniques. These show a small but significant preference for nasal-ward motion, however there is no evidence of a vertical motion preference asymmetry [23] [24]. In subjects with strabismus a motion preference asymmetry for nasally directed motion is seen in both the squinting and non-squinting eyes. The magnitude of this asymmetry appears to be related to the angle of the squint [25]. The effects of central and peripheral retinal stimulation on motion perception are similar in both normal subjects and those with infantile esotropia [26], however the mean detection thresholds for motion are higher in subjects with infantile esotropia when compared with healthy control subjects [27]. Binocularity also plays a role in motion processing since those individuals with poor binocularity have impaired motion processing [28]. Interestingly, the vestibulo-ocular reflex also has an effect on motion perception since it is found that individuals suffering from laryrinthine defects have raised detection thresholds. This is possibly a perceptual-adaptive compensatory mechanism to reduce the symptoms of oscillopsia caused by the resultant nystagmus [29].

Animal models looking at the topographical organization of the primate cortical visual system suggest that six groups of direction sensitive cells exist in the primary visual cortex, V1. One group in each hemisphere, possibly in layer 5, project directly to the nucleus of the optic tract (NOT), whilst the other 4 groups located in layer 4B pass indirectly to the NOT [30] via the extra-striate areas, the middle temporal area (MT also known as V5) and the medial superior temporal visual area (MST or V5A) [31]. The primary visual cortex (V1) is also linked to a cluster of prestriate areas including V2, V3, VP, V4t and V3A. Projections pass from these regions to areas including the MST (or V5A) and MT. Both the MT and the MST seem to be involved in motion perception [32] and communicate with each other through the corpus callosum [30]. Their receptive fields are larger and more directionally selective for motion at higher speeds than area V1 [33]. The MT and the MST subsequently sends projections to the parietal lobe where they are thought to be the key to extra-striate motion processing [34].

Functional MRI (fMRI) studies (figure 1.1) on adult volunteers corroborate the findings of animal studies and locate the human homologue of area MT and other components of V5 in the occipito-temporal cortex [35], in particular at the boundary of Brodmann's areas 19 and 37 [36].

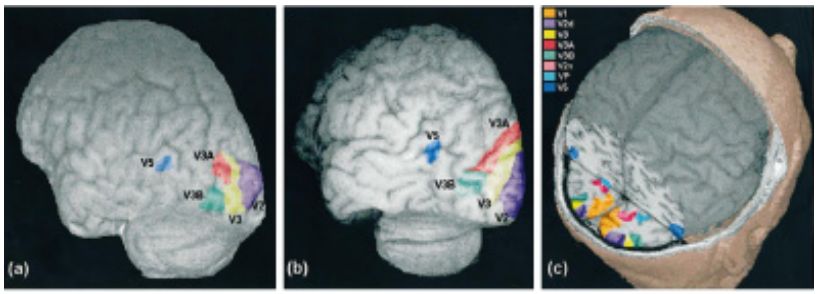
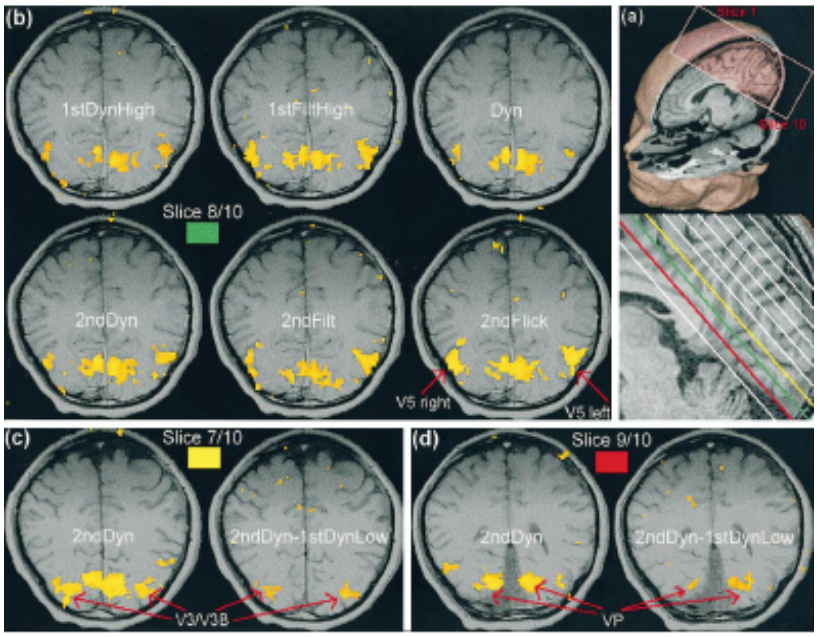


Figure 1.1: *3-D Images of some of the visual areas activated during OKN*
(a) & (b) show the surface of the left hemisphere
(c) shows image (b) with part of the cortex cut away



Functional activation of the brain.
(a) & (b) represent different slices of the cortex
(b) shows activation in V1 and V2v medially, whilst bilateral activation is evident in V5

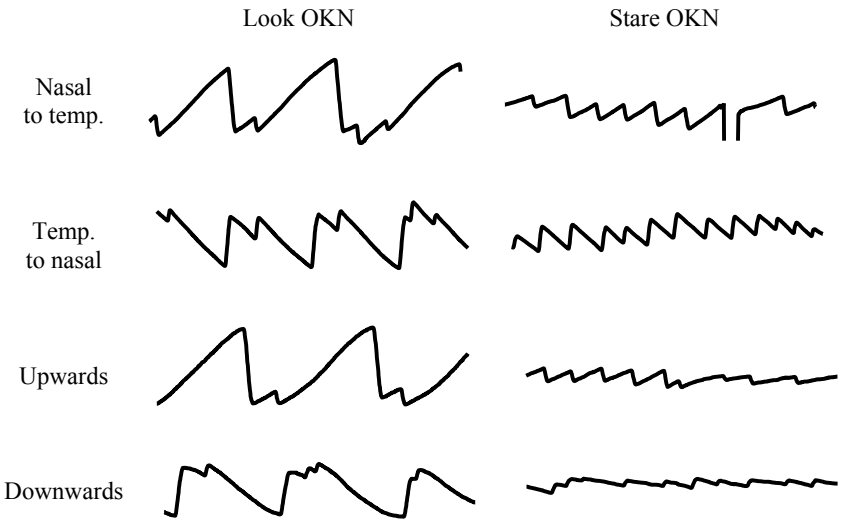
(c) shows activation in area V1 medially and activation in V3 bilaterally

Reproduced from 'Brainstem and cerebellar fMRI-activation during horizontal and vertical OKN stimulation' . Smith AT et al, The Journal of Neuroscience, 1998: 3816-3830

1.3 Optokinetic Nystagmus (OKN)

Optokinetic nystagmus (OKN) is a reflex eye movement induced by motion of the whole or a large proportion of the visual field [37]. It consists of two basic components, a slow tracking movement and a rapid recovery / resetting quick phase [38], and supplements the vestibular-ocular reflex (VOR) during rotational head movements [39] . Two forms of OKN are said to exist, 'look' and 'stare' OKN (figure 1.2), which were first described by Ter Braak in 1936 [40]. 'Look' OKN is characterized by a high gain, large amplitude slow phase with infrequent quick recovery phases. Typically it is elicited by asking an observer to actively fix and follow a single detail on a moving OKN target stimulus [37]. 'Look' OKN is thought to be under cortical control [41-43] and related to the smooth pursuit system. 'Stare' OKN on the other hand is of low gain and amplitude with frequent fast recovery phases [37]. It is thought to be under sub-cortical control [41] and results when a subject passively fixates on the centre of an OKN target stimulus.

***Figure 1.2**: An example of raw 'look' and 'stare' OKN data*



It is important to distinguish OKN from smooth pursuit. This is a continuous voluntary rotational movement of the eye that allows an individual to selectively track motion signals of interest in the visual field despite the presence of alternative stronger motion signals in other directions. It allows the eyes to compensate for object motion and

minimize image blur [44 45]. Smooth pursuit can be influenced by cognitive expectations which in some cases can drive pursuit in the absence of a visual stimulus, for example when anticipatory responses are made during observation of a repeated motion target stimuli [44]. Despite the fact that smooth pursuit (voluntary) and OKN (reflex) are different types of eye movement, it is possible that the same nuclei and neurons are involved in their generation [46].

1.3.1 Neurological control of OKN

Experimental models suggest the control of OKN is complex. In the case of horizontal OKN, the most extensively investigated form of OKN, there are two sub-components, an early fast (direct) response, OKNe and a delayed slow (indirect) response OKNd [2 37]. Both appear to be influenced by the cerebellum, since lesions to the flocculus in monkey models result in altered OKNe responses, whilst lesions affecting the nodulus and uvula affect OKNd [2]. Typically OKNe has a rapid build up of velocity and is mediated by a cortico-ponto-cerebellar neural pathway (cortical), which projects to the oculomotor centres. OKNd on the other hand is characterised by a slow build up of velocity and persists in the dark as optokinetic after nystagmus (OKAN) [2]. This is highly asymmetric with reduced downward responses [47 48] and is thought to be related to the vestibulo-ocular response, since it has a similar velocity storage component and response characteristic to the vestibulo-ocular reflex [2]. In evolutionary terms, OKNd is assumed to be the older of the two forms of OKN [49]. The relative contribution of the early and delayed systems varies from species to species, with the OKNd system dominating in animals with poor or no foveal vision, whereas humans, with a well-developed fovea have OKN dominated by OKNe responses in photopic vision. The only evidence of OKNd in humans is the presence of OKAN [39 50], which appears to be exclusively associated with stare OKN and not look OKN [51].

The main four nuclei responsible for the generation of OKN are the dorsal terminal nucleus (DTN), lateral terminal nucleus (LTN) and medial terminal nucleus (MTN) which are grouped together and are collectively known as the accessory optic system (AOS). The fourth nucleus, the nucleus of the optic tract (NOT) is found in the pretectum of the midbrain.

The majority of the research relating to the AOS and NOT has been carried out on animal models due to the invasive nature of the studies. However since the anatomy and physiology of these nuclei appear consistent across a wide range of mammals, it would seem reasonable to assume that a similar arrangement exists in the human brain [52 53]. These studies indicate that the NOT receives afferent fibres from the retina, the striate cortex (V1), the prestriate cortex (V2, V3, V4, MT and MST), the frontal motor areas including the frontal eye fields, supplementary eye fields and the parietal areas and the superior colliculus. Projections pass to the medulla, pons, AOS, ocular motor nuclei and cerebellum [52]. Whilst the AOS receives input from the retina, the visual cortex, the NOT, MT and MST and the diencephalon (including the thalamus and hypothalamus). Efferent fibres pass to the cerebellum, the pons and the medulla, including the vestibular nuclei [53]. Animal studies indicate that both the AOS and NOT consist of predominantly GABAergic neurons and that these play a significant role in the generation of OKN [53].

Anatomically the AOS and NOT are so closely connected that they act as a single operational unit, with the result that there are three functional groups of neurones responding to the different directions of motion [2]. The AOS in each hemisphere are interconnected with each other and play a role in determining the direction of OKN. It is possibly the site where inhibitory responses between retinal afferents synapse [2]. All four nuclei responsible for OKN communicate with each other [54 55] producing a single coordinated response to a number of different visual stimuli [2].

Studies looking at the generation of horizontal OKN [56] in higher organisms suggests cortical (indirect) inputs to the NOT are driven by either eye, whereas direct retinal inputs are derived from the contralateral eye [57]. The majority of nuclei in the NOT receive input from the contralateral eye with about half of them also receiving ipsilateral input (binocular input). Activation by the contralateral eye tends to be stronger in the binocular units [58]. Nuclei with a large receptive field seem to respond preferentially to motion directed towards the ipsilateral side, whereas motion in the opposite direction results in inhibition.

In essence retinal information passes directly and indirectly via the visual cortex, to relay with the NOT (figure 1.3) [57], which is thought to provide direction-selective information about retinal slip during OKN [59 60].

All vertebrates are thought to share a similar subcortical mechanism to produce OKN [2].

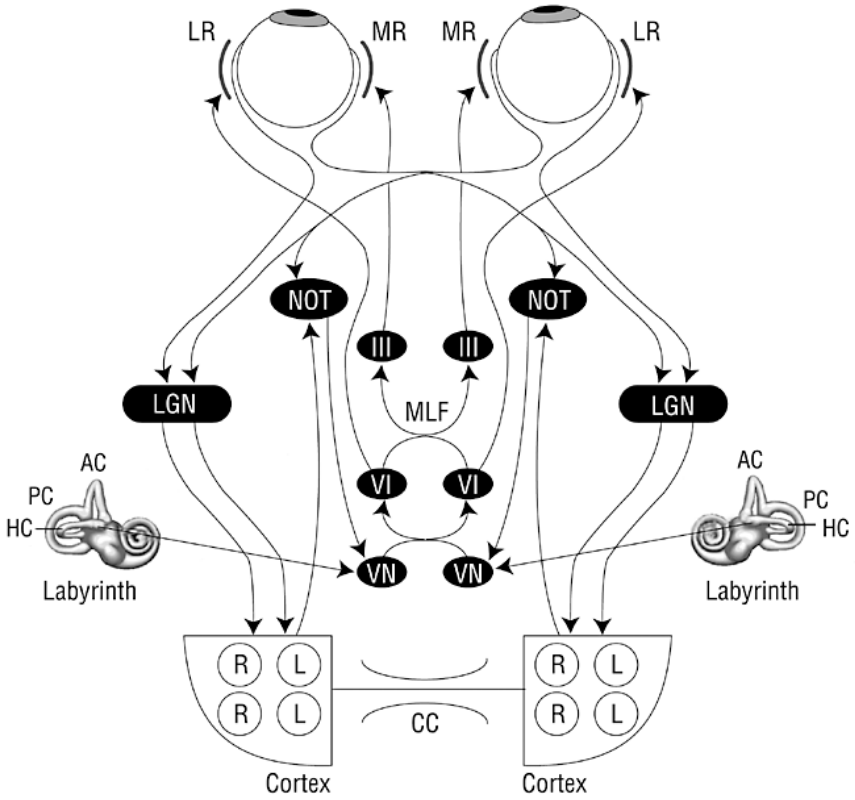


Figure 1.3: *A schematic diagram depicting cortical and subcortical optokinetic pathways. Cortical input to temporally directed movement, which is present only in frontal-eyed animals, requires the establishment of normal binocular cortical connections. This input is absent in humans with congenital strabismus. Direct crossed pathways from the eye to the nucleus of the optic tract provide nasalward subcortical optokinetic responses even when binocular cortical connections are absent (R and L represent monocular cortical cells corresponding to the right and left eyes, respectively). Note that the nucleus of the optic tract (NOT) relays horizontal visuo-vestibular information to the vestibular nucleus (VN), where it is integrated with horizontal vestibular input from the labyrinths to establish horizontal extraocular muscle tonus. LGN indicates lateral geniculate nucleus; CC, corpus callosum; V1, abducens nucleus; III, oculomotor nucleus; LR, lateral rectus muscle; MR, medial rectus muscle; AC, anterior canal; PC, posterior canal; and HC, horizontal canal. Reproduced from Latent Nystagmus: Vestibular Nystagmus with a Twist. Brodsky MC et al, Archives of Ophthalmology, 2004: 202-9.*

In primitive animals the majority of information passed to the NOT are via crossed afferent retinal fibres and project directly to the NOT. This results in OKN with a nasal-ward preference [2 61]. In higher organisms such as cats, primates and humans, information detected by the retina also has uncrossed indirect communication with the NOT via the visual cortex (fig 1.3). The direct retinal pathways originate in the nasal retina and show a high temporal to nasal sensitivity whereas indirect pathways originate from the temporal retina with a high nasal to temporal sensitivity [2 62 63]. The result is that temporal motion is generated equal to that of nasal motion, producing OKN responses with no asymmetry. Cortical lesions result horizontal OKN asymmetry with a preference for nasal-ward directed motion [64].

Hoffmann et al [65] proposed that in adults, the input from the visual cortex dominates OKN, whereas in neonates, it is the direct retinal input which predominates thus explaining the nasal OKN asymmetry seen in very young children. This hypothesis is supported by **Morrone at al** [66] who found that OKN asymmetry evolved over time with decreasing emphasis on direct OKN pathways even in human infants with severe unilateral cortical damage.

The LTN and MTN seem to be associated with vertical OKN in mammals [67-69]. The cells in the LTN are selective for either upward or downward motion. Those responsible for upward motion seem to receive indirect input from the ipsilateral visual cortex, whereas those cells responsible for downward motion appear to be influenced by direct pathways from contralateral retina [70 71]. Upward selective cells appear to be tuned to higher velocities [70].

Functional magnetic resonance imaging (fMRI) studies have been used to identify areas of the normal human brain involved in producing OKN responses. **Bucher et al** [72] found that whilst viewing horizontal OKN target stimuli, test subjects show bilateral activation of both the cortical and subcortical areas of the brain including the primary visual areas (Brodmann area 17), the motion sensitive areas in the occipito-temporal cortex and the cortical ocular motor centres responsible for the control of saccadic eye movements (the parietal eye field, the frontal eye field, the prefrontal cortex and the supplementary eye field). **Dieterich et al** [73] found similar patterns of activation when investigating vertical and horizontal OKN with a distinct right hemisphere dominance.

Interestingly studies by **Dieterich et al** and **Bense et al** looking at the cerebellum [74 75] during vertical and horizontal OKN stimulation reveal bilateral activation of the cerebellar hemispheres, middle cerebellar peduncle and the cerebellar nuclei (the dentate nucleus, uvula and the culmen/pyramid of vermis). The authors suggested that the activity in the cerebellar hemispheres was associated with changes in attention, whilst the vermal activity was associated with ocular motor control. The responses seen in the dentate nuclei and cerebellar peduncles were thought to be associated with both attention and oculomotor control. These fMRI findings seem to suggest that similar structures are involved in the initiation and control of vertical and horizontal nystagmus.

1.3.2 Horizontal OKN

Horizontal, vertical and torsional OKN all demonstrate the same characteristics of a slow tracking phase followed by a rapid resetting saccade. Of these three forms of OKN, horizontal OKN is the most widely investigated and there is general agreement that there is no horizontal OKN asymmetry in normal healthy adult subjects [37].

A physiological horizontal OKN asymmetry is however seen in infants [76-78] with a temporal to nasal preference, although with increasing maturity the OKN responses eventually become symmetrical. This occurs between 3 to 5 months of age [76 77 79-83]. **Lewis et al** [84] investigated 'OKN acuity', that is the narrowest stripe able to elicit OKN in infants, and found an asymmetry to high frequency stimuli in infants up to 18 months of age. The authors suggested that OKN asymmetry declined during this period due to rapid improvements in OKN acuity, especially for temporally directed stimuli, when compared with nasally directed stimuli. Other species, such as the cat or primate, develops symmetrical OKN much sooner than human infants [10]. Kittens are found to have nasally directed OKN at approximately 3 weeks of age, with temporally directed OKN developing one week later [85].

Wattam-Bell et al [24] looking at motion preference and OKN found no evidence of a vertical OKN asymmetry in human infants.

A horizontal OKN asymmetry can also be seen in subjects whose visual development and binocularity has been arrested in infancy and early childhood. Typically these subjects suffer from amblyopia, a form of cerebral visual impairment in the absence

of an organic cause [86 87]. The types of visual deprivation leading to amblyopia include anisometropia, strabismus, congenital cataract, and any other condition reducing the clarity of an image in one or both eyes. Amblyopia can be characterised by a range of deficits in spatial vision, which can be demonstrated by reduced visual acuity and contrast sensitivity [87-90], the extent of which seems to depend upon the type of amblyopia. Clinically it can be diagnosed when there is a difference in the corrected visual acuity between both eyes of 2 or more lines on a visual acuity chart [91]. Treatment is only thought to be effective during the first 7 to 8 years of life when the visual system is developing [86].

The horizontal OKN asymmetry seen in subjects with amblyopia show a preference for nasally directed stimuli in both the amblyopic and non-amblyopic eyes [10 92-98]. The age of visual disruption appears to play an important role in the aetiology of the horizontal OKN asymmetry, since children whose visual development is arrested after the age of three have symmetrical OKN in both eyes [99]. **Reed et al** [93] compared 4 groups of subjects; early onset strabismus (before 24 months of age), late onset strabismus (after 24 months of age), monocularly enucleated subjects and a normal control group. Subjects with early onset strabismus were found to have a statistically significant horizontal OKN asymmetry, whereas individuals with later onset strabismus (after 24 months of age) had symmetrical OKN response, as did subjects who were monocular following enucleation of the fellow eye, irrespective of the age at enucleation. **Shawkat et al** [100] subsequently investigated the effect of profound and non-profound unilateral loss of vision on OKN. No OKN asymmetry was seen in subjects monocular from birth (profound), whereas those infants monocularly aphakic (non-profound) had OKN asymmetry with a nasal preference. These findings suggest that OKN asymmetry in strabismic and amblyopic individuals are due to abnormal binocular competition between both eyes [93 100] from an early age. In normal subjects there would be complete binocular competition, whereas in monocular individuals, there will be no competition.

Westall et al [94] investigating the effects of the age of onset of strabismus on OKN found a high proportion of subjects (73%) with early onset strabismus (before 24 months of age) had an OKN asymmetry (bilateral in 37% of cases), whilst those with a later onset of strabismus, had asymmetry (42%) predominantly confined to the deviating eye. The

authors compared asymmetries in both deviating and non-deviating eyes following patching treatment, slight improvement in OKN asymmetry was seen in the deviating (non-dominant eye). **Westall et al** [95] subsequently found that infants and toddlers with an onset of strabismus before the age of 6 months (infantile esotropia) all had OKN asymmetries in the deviating eye (bilateral in 93%). Whilst **Demer et al** [101] also investigating the effects of the age of onset of strabismus on OKN in three subject groups, those who developed strabismus between the ages of 0 and 6 months, 6 to 12 months and over 24 months. They found that OKN asymmetries were more commonly associated with early onset strabismus. The youngest group was associated with the highest proportion of OKN asymmetry (58%) and the eldest group with the lowest (5.3%). **Brosnahan et al** [92] also found OKN asymmetries were associated with early onset strabismus. 60% of subjects who developed a strabismus before one year of age had an OKN asymmetry, which was bilateral in 30% of cases. Onset after 1year of age was only associated with an asymmetry in 33% of cases (bilateral in 9%). Further evidence that the age of onset of strabismus affects horizontal OKN asymmetry comes from **Steeves et al** [96] who investigated OKN in young adult subjects (mean age 20 years) with a horizontal strabismus. Those subjects who developed strabismus before 24 months of age were associated with larger OKN asymmetries than those with later onset strabismus (after 24 months). Asymmetries were seen in both the deviating and non-deviating eyes, however the deviating eye had the highest incidence of an asymmetry. Interestingly the normal control group had a small but significant OKN asymmetry with a preference for nasal motion.

Valmaggia et al [98] investigated the relationship between OKN asymmetry and the binocular vision. Four groups were investigated; no binocularity, poor binocularity, good binocularity, and normal controls. A significant temporal to nasal OKN asymmetry was found in the group of subjects with no evidence of binocular vision. This was greater in the presence of a dissociated vertical deviation (DVD). Asymmetries were more common in the non-dominant eye. The other subject groups showed no evidence of asymmetry, however in the groups with poor binocularity the gains were reduced when compared with normal individuals. Further work by **Valmaggia et al** [102] investigated the effect of binocularity on the symmetry of ‘look’ and ‘stare’ OKN in 10 volunteers with no

binocular vision and 20 control subjects. In those subjects with no binocular vision a nasal-ward preference was seen with both 'look' and 'stare' OKN responses. This asymmetry was not present in controls. **Wright et al** [103] also investigated the effects of binocularity on OKN asymmetry by examining four subject groups; a control group and 3 different groups with esotropia. These 3 groups consisted of; one with congenital esotropia surgically corrected within the first few weeks of life and good stereopsis, a second group with congenital esotropia treated after the age of one year and no stereopsis and a third group of subjects with acquired hypermetropic esotropia developing after 2.5 years of age and corrected with full-time spectacle wear with good binocular vision. The two groups with congenital esotropia had evidence of an OKN asymmetry. The control and late onset strabismus group had no evidence of an asymmetry.

1.3.3 Vertical OKN

Vertical OKN is not as widely investigated as horizontal OKN and the asymmetry results are more varied. There is no accepted vertical OKN asymmetry although the majority of reports in the literature describe a preference for upward stimuli [38 41 104-107]. However a number of studies report a preference for downward stimuli [108] and some find no OKN asymmetry at all [109-111]. The issue is further confounded by the fact that symmetry of vertical OKN is dependant on several visual and vestibular influences such as the degree of central and peripheral field stimulation [39] and the direction of gravity with respect to the head [47 112] (see table 1.1 for a summary of the vertical OKN literature).

The first report concerning vertical OKN asymmetry in the literature was by **Collins et al** [111] in 1970 who found there was no asymmetry in ten healthy individuals. It is unclear what target stimuli and recording techniques were used. **Jung et al** [113] in 1971 reported a downward asymmetry (a higher gain in a downward direction) using electro-oculogram (EOG) recording techniques. Several years later, in 1978, **Takahashi et al** [106] found an upward vertical asymmetry in twenty subjects at velocities of 70°/s and greater also using an EOG recording technique. The target stimuli were produced by projecting the image of a rotating drum with 12 vertical slits cut into it on to a white semi circular screen and presented at a variety of speeds ranging from 0°/s to 200°/s. Subjects were healthy adults aged between 17 and 50 years.

In 1980 **Schor et al** [114] found a slight downward OKN preference in 2 out of 5 healthy subjects who viewed a sinusoidal grating of 1 cycle/degree, luminance of 1cd/m^2 and contrast of 80% at a velocity of 6°/s. The target was shown on an oscilloscope screen (8° x 10°) at a working distance of 71cm. Infra-red eye movement recording techniques were used to record the eye movement data. Further studies by **Schor et al** [108] looking at the effects of spatial frequency and field size on OKN in a small group of subjects found a downward OKN asymmetry in one of 3 healthy adults. Sinusoidal and square wave gratings ranging from 0.5 to 16 cycles/degree were viewed at 1m (visual angle 2° x 1.6°), 67cm (10° x 8°), and 15cm (45° x 36°) on a cathode ray tube with a contrast of 80% with a luminance of 10cd/m^2. Target velocity ranged from 1.5°/s to 60 °/s. Increasing stimulus size seemed to be correlated with increased slow phase velocity.

A downward vertical asymmetry was also described by **Baloh et al** [110] in 10 subjects using EOG recording techniques. These results were not of statistical significance. Each subject viewed a large optokinetic drum 1m in diameter with 2.5cm wide vertical white stripes spaced at 15.6° intervals separated by a black background. A peak target velocity of 60°/s was investigated. Vertical OKN was measured by tilting the observers' chair laterally so the observers' head was at 90° to the vertical axis. In this unusual position the effect of gravity on the middle ear may well have had a confounding effect on the OKN asymmetry.

In an interesting paper by **Hainline et al** [109] the 'stare' OKN responses of 7 healthy adults and 16 infants were compared. An upward asymmetry was seen in the infant group (age range 22 to 114 days), whereas the in the adult group (age range 18 to 36 years) there was no vertical asymmetry. OKN targets consisted of sinusoidal and square wave grating stimuli with a spatial frequency of 0.3 cycles/degree and a contrast of 70%. Target velocity was 7°/s. The stimuli were produced on a cathode ray tube at 78cm with a visual angle of 30° x 22°. Eye movement recordings were made using an infra-red corneal reflection video system. Regression analysis of the infant subject group data suggested that slow phase amplitude and gain in the downward direction increased with age. The authors postulated that this vertical OKN asymmetry seen in infants was a result of problems encountered in coordinating information between the two hemispheres of an immature brain.

To assess the effect head position on vertical 'look' OKN **LeLiever et al** [105] measured the OKN responses of 21 volunteers whilst they sat in an upright position, tilted laterally on one side and in a head hanging position. The target stimuli used during this series of investigations was produced by projecting the image of an 'optokinetic cage' with slats spaced to provide 10 degree light and dark stripes on to the inside of a fibre glass hemispherical screen. Four target velocities were investigated; 40°/s, 50°/s, 60°/s and 70 °/s with the head in the upright position and 3 velocities; 40°/s, 50°/s and 60°/s with the subject tilted laterally and in the head hanging position. Recordings were made using an EOG technique. A downward asymmetry was seen for target velocities of 50°/s whilst the subject sat in an upright position. For all other target velocities, no asymmetry was seen. **Calhoun et al** [115], also using EOG recording techniques, measured the OKN of 17 subjects whilst sitting upright and laying semi-prone with their right ear facing the ground. The target stimulus was projected on to a tangent screen subtending 92° at 70 cm and consisted of black (5°) and white (1°) stripes moving horizontally or vertically at 20 °/s. Overall no vertical OKN asymmetry was seen in either an upright or semi-prone position.

Using a more sensitive magnetic search coil technique to record eye movements **van den Berg et al** [107] found an upward asymmetry in 7 volunteers. The target consisted of random dot OKN stimuli, which were projected on to a hemispherical projection screen with a radius of 80cm. Four different target velocities; 9°/s, 23°/s, 36°/s and 57°/s were investigated.

The sensitivity of different areas of the retina to vertical OKN stimuli were investigated by **Murasugi et al** [39] in 1989. Ten healthy subjects (age range 24 to 60 years) were assessed whilst their eye movements were recorded using magnetic search coil techniques. Target stimuli consisted of a random dot pattern. Each dot subtended 2° and with a density of 450 dots/m^2, they were projected on to tangent screen of 61° x 64° at 57cm. The stimulus velocities investigated were 10°/s, 30°/s, 50°/s and 70°/s with a contrast of 95%. OKN generated by the peripheral retina was assessed by masking the centre of the target screen with a vertical 3°or 6° wide occluder. To assess the effects of central retinal stimulation both ends of the target stimuli were masked by 2 occluders leaving a vertical 6° wide strip exposed. Centre only OKN was measured using a smaller

centrally located 10° x 6° OKN target. Full screen OKN was also assessed. Overall, full screen stimulation resulted in an upward asymmetry for velocities of 30°/s and over. No asymmetry was seen at 10°/s. Occlusion of the central area of the retinal resulted in OKN responses with reduced downward motion and unaffected upward responses (upward asymmetry). Stimulation with the central 6° wide target strip resulted in OKN responses similar to those produced by full field stimulation. No asymmetry was seen with the small central 10° x 6° OKN stimulus. The authors concluded that OKN resulting from stimulation of the peripheral retina was responsible for vertical OKN asymmetry.
Other factors thought to have an influence on vertical OKN, due to its association with VOR [39], were the effects of gravity on the inner ear. **Clémant et al** [41] assessed the OKN responses of subjects positioned in three different orientations; upright, 90° roll and up-side down using EOG techniques. Target stimuli consisted of a 180° random dot pattern presented horizontally and vertically to upright observers, whilst a second stimulus was generated on a portable binocular system and used to record OKN with the subject lying at 90° and hanging upside down. For this, the pattern consisted of a black and red checkerboard (4° per square) of 115° x 110° and was viewed through Fresnel prisms. Three different stimulus velocities; 27°/s, 39°/s and 51°/s were investigated. An upward OKN asymmetry was seen with stimulus velocities of 39°/s and 51°/s whilst the subject was seated in an upright position. Two subjects exhibited a reversal of vertical OKN asymmetry when suspended upside down. Vertical asymmetry and OKN gain were decreased with the subject lying at 90°. The author suggested this was the result of disorientation rather than a direct effect on the OKN mechanisms.

In 1996, **Ogino et al** [104] found an upward OKN asymmetry in 20 healthy volunteers who viewed an OKN target of alternating black (24 °) and white (4°) stripes projected onto a hemispheric screen 80cm in diameter. Seven velocities were investigated; 30°/s, 40°/s, 50°/s, 60°/s, 70°/s, 80°/s and 90°/s. Upward gains appeared to increase with an increase in stimulus velocity from 30°/s to 40°/s (maximum at 40°/s and at 50°/s) and then decreased with higher stimulus speeds. Interestingly downward gains varied only slightly with a change in the stimulus velocity.

A meeting abstract by **Proudlock et al** [116] in at ARVO (2001) describes an upward preference in 25 adult subjects using infra-red eye tracking techniques. Stimulus

velocities of 10°/s, 20°/s and 40°/s were investigated. These findings were supported **Garbutt et al** [38] in 2003 who found a preference for stimuli moving upwards in 10 subjects aged between 24 and 54 years. Target stimuli consisted of alternating black and white stripes at spatial frequencies of 0.04, 0.08 and 0.16 cycles/degree. The target had a luminance of 0.7 and 13.7 cd/m^2 (black and white stripes) and was projected on to a tangent screen 72° x 60 ° at 1m. Six velocities were investigated; 10°/s, 20°/s, 30°/s, 40°/s, or 50°/s.

Table 1.1: *Summary of the vertical OKN literature:*

Author	Subjects	Look / Stare OKN	Asymmetry	Recording Technique
Collins et al [111]	10	Unknown	None	Unknown
Jung et al [113]	Unknown	Unknown	Downward	EOG
Takahashi et al [106]	20	Unknown	Upward	EOG
Schor et al [114]	5	Unknown	Downward	Infra-red
Schor et al [108]	3	Unknown	Downward	Infra-red
Baloh et al [110]	10	Unknown	Downward	EOG
Hainline et al [109]	7 Adults 16 Infants	Stare	None Upward	Infra-red
LeLiever et al [105]	21	Unknown	Downward	EOG
Calhoun et al [115]	17	Unknown	None	EOG
van den Berg et al [107]	7	Unknown	Upward	Search Coil
Murasugi et al [39]	10	Unknown	Upward	Search Coil
Clémant et al [41]	6	Look	Upward	EOG
Ogino et al [104]	20	Unknown	Upward	Unknown
Proudlock et al [116]	25	Unknown	Upward	Infra-red
Garbutt et al [38]	10	Unknown	Upward	Search Coil

1.3.4 The effects of target change on OKN gain

With the exception of the study by **Murasugi et al** [39] (described in section 1.3.3 'vertical OKN) there are very few studies investigating at the effects of different target size, shape and luminance on vertical OKN.

The effects of target change on horizontal OKN are more clearly understood. **Van Die et al** [117] investigated the effect of a central scotoma on horizontal OKN gain in 10 healthy volunteers. The target consisted of a full screen OKN target stimulus (180° x 105°) with a 10° occluder placed in the centre of the screen to produce a central artificial scotoma. A second target, a full screen OKN target (180° x 105°), was used as a control.

The artificial scotoma in the centre of the stimulus resulted in reduced horizontal OKN gains [117]. Interestingly when a 10° target was used to stimulate the foveal region of the retina, the gain was only slightly reduced compared with the full screen stimulus. Hemi-field stimulation, also investigated, produced OKN responses with reduced gains, as well as an OKN asymmetry with a preference for targets moving towards the fovea (foveopetal motion) [117].

Further work by **Van Die et al** [118] investigated the effects of visual field masking, light intensity and ocular pathology on horizontal OKN. Under scotopic conditions where vision is predominantly rod driven, subjects have a central physiological (scotopic) scotoma. The OKN responses under these conditions show reduced gains when compared with targets viewed under photopic conditions. Subjects with a pathological central scotoma such as age related macular degeneration have reduced horizontal OKN gains [118]. The authors also found that masking the horizontal boundaries of OKN targets only had a small effect on horizontal OKN gain when compared with masking a vertical boundary, which cause a modest decrease. These findings were supported by **Abadi et al** [119] who investigated the effects of simultaneous central and peripheral field stimulation on OKN in 6 normal healthy volunteers. Full field and central field stimulation elicited OKN of similar magnitude, whilst peripheral stimulation resulted in significantly reduced OKN. Central and peripheral OKN stimuli moving simultaneously in opposite directions, reveal central dominance. When the two stimuli moved simultaneously in the same direction at different velocities, the OKN response was governed by target velocity, rather than stimulus position, with the slower of the 2 stimuli governing the response.

Valmaggia et al [120] attempted to quantify the effects of central scotoma size on OKN gain in subjects with age related macular degeneration. Central scotomas of 1 -10 ° and 10 -20 ° had gains that were not significantly different from a control group of normal subjects, however with a larger scotoma of 20°-30° OKN gains were significantly reduced at stimulus velocities of 30°/s, 45°/s and 60°/s. **Howard et al** [121] also found that central occlusion (scotoma) only reduced horizontal OKN gains at stimulus velocities of 30°/s and above. It was suggested that horizontal OKN is driven more effectively by the central retina and that different control mechanisms were responsible for the high and low velocity OKN responses. The authors postulated that high velocity OKN was driven by

indirect cortical connections to the nucleus of the optic tract (NOT), whilst at low velocity, OKN was driven by direct retinal connections [121].

OKN also seems to be sensitive to target contrast levels. **Leguire et al** [122] investigated the effects of contrast on horizontal OKN responses for 5 OKN stimuli of different spatial frequency in 3 normal subjects. They found that with gratings of increasing spatial frequency, there was an initial increase in contrast sensitivity (reciprocal of threshold), before it decreased at higher frequencies. The pattern was similar to those results achieved with psychophysical methods for measuring contrast sensitivity. No difference was found for stimuli moving in a nasal or temporal direction.

1.3.5 The effects of Parkinson's disease on OKN

Idiopathic Parkinson's disease is the second most common neurodegenerative disorder after Alzheimer's disease. Its pathology is spread throughout the central nervous system [123] and can be seen microscopically as a loss of pigmented neurons in the basal ganglia and an accumulation of Lewy bodies (eosinophilic proteinaceous intracytoplasmic inclusions) throughout the brain [124 125].

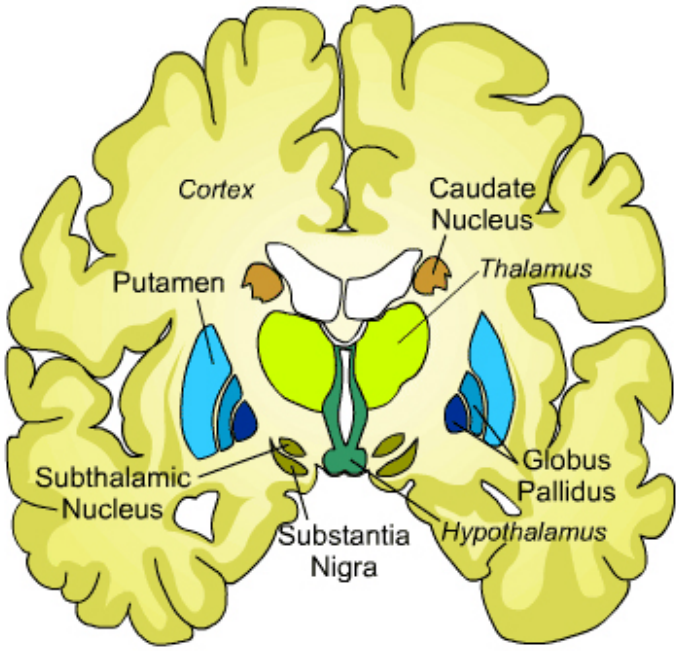


Figure 1.4: *The basal ganglia. Reproduced from 'Scienceblogs.com'.*

The basal ganglia (figure 1.4) are involved in large cortico-basal ganglia-thalamo-cortical loops, including the oculomotor loop, which interact with the frontal eye fields and parietal posterior cortex before projecting to the superior colliculus, where it is thought to be involved in the generation of saccades. Another loop, the dorsolateral prefrontal loop, may play a role in memory guided tasks including saccade generation [7]. There is also evidence that the subthalamic nucleus of the basal ganglia process and regulate information related to eye movement, and that it subsequently relays with the other structures in the basal ganglia [126 127]. No smooth pursuit pathways have been demonstrated through the basal ganglia [128].

Functionally Parkinson's disease is characterized by loss of dopaminergic neurons in the substantia nigra pars compacta of the basal ganglia and the locus caerulus [129-131] with a reduction in striatal dopamine. The net result of this is a disruption of the normal balance that the dopaminergic and cholinergic systems exert over GABAergic cells in the corpus striatum. Under normal circumstances the dopaminergic neurons inhibit the GABAergic system whereas the cholinergic system exerts an excitatory effect.

Drug treatment of Parkinson's disease is aimed at restoring the balance of the dopaminergic and cholinergic systems. Unfortunately dopamine cannot be used to treat Parkinson's disease since it does not cross the blood brain barrier, however a metabolic precursor levodopa does. This is decarboxylated to dopamine by dopa decarboxylase and is used in the treatment of Parkinson's disease. Decarboxylation of levodopa not only occurs in the brain, it can also occur in the peripheral blood system before it reaches its target in the brain. To overcome this levodopa can be administered with a peripheral decarboxylase inhibitor in the form of co-beneldopa (levodopa and benserazide hydrochloride) or co-carelodopa (Levodopa and carbidopa). Unfortunately this inhibition of dopa decarboxylase can result in the activation of other pathways that metabolize levodopa to dopamine, in particular catechol-O-methyltransferase (COMT). COMT inhibitors such as entacapone are therefore used to increase the effectiveness of levodopa in the treatment of Parkinson's disease. The effects of levodopa can also be enhanced by selective inhibition of monoamine oxidase B with drugs such as selegiline.

Where the ability of the brain to synthesize dopamine (and convert levodopa to dopamine) is reduced, direct dopamine agonists can be used to treat Parkinson's disease.

These drugs act on the five different dopamine receptors which exist throughout the brain (D_1 -like (D_1, D_5) and D_2 -like (D_2, D_3, D_4)). The majority of the dopamine agonists currently in use have a preference for D_2 –like receptors [125]. These drugs include: bromocriptine, pergolide, cabergoline, lisuride, pramipexole, ropinirole and apomorphine a potent dopamine agonist. Amantadine, an antiviral agent, is also used in Parkinson' disease however its' antiparkinsonian effects are mediated through an unknown mechanism of action.

Other ways to try to restore the dopamine / cholinergic imbalance are to suppress the cholinergic system with antimuscarinic agents such as benzatropine mesilate, procyclidine and orphenadrine [125 132].

Clinically, patients with Parkinson's disease display to varying degrees, a combination of; resting tremor, plastic rigidity, delayed initiation of movement, slowness, and impaired postural and righting reflexes. In advanced disease there is cognitive decline, depression and autonomic sensorimotor dysfunction [125], eventually resulting in dementia [133]. Its' severity can be classified by the degree of physical disability using the Hoehn and Yahr scale [134];

- **Stage I** - Unilateral involvement only with minimal or no functional impairment.
- **Stage II** - Bilateral or midline involvement, without impairment of balance.
- **Stage III** - First sign of impaired righting reflexes. Evident by unsteadiness on turning or demonstrable on pushing a patient when standing with the feet together and eyes closed. Functionally patients are restricted their activities, but may have work potential depending upon the type of employment. Patients are physically capable of leading independent lives. Disability is mild to moderate.
- **Stage IV** - Fully developed severely disabling disease. The patient is able to walk and stand unassisted but is markedly incapacitated.
- **Stage V** - The patient is confined to bed or a wheelchair unless aided.

As well as the systemic effects associated with Parkinson's disease, eye movements and vision are also affected. In a study of early onset untreated Parkinson's disease, visual hallucinations were reported along with an increased incidence of ocular surface irritation, blepharospasm, reduced blink rates and reduced amplitudes of

convergence [135]. In later stages of the disease patients can suffer from apraxia of lid opening [136]. The vestibulo-ocular reflex is normal in Parkinson's disease [3].

Oculomotor defects associated with Parkinson's disease include a diminished ability to generate volitional / memory guided saccades which can be demonstrated as delayed reaction times during anti-saccade tasks. Interestingly memory guided saccades are almost normal if the memory period is prolonged to around 30 seconds, suggesting there may be two pathways involved in the generation of these saccades, a short one involving those structures affected by Parkinson's disease and a longer one bypassing them [137]. Visually guided / automatic saccades are less affected than memory guided saccades, however the ability to suppress them is reduced [129 130].

Smooth pursuit is reduced in Parkinson's disease, particularly in the more severely affected individuals, where smooth pursuit gains are significantly impaired [138-140]. It is possible that these changes are a result of abnormal doperminergic innervation, however the effects of treatment with levodoa on smooth pursuit are inconclusive [138 140 141]. Apomorphine, a short acting dopaminergic agent more potent than levodopa, has demonstrated some improvement in a small number of subjects [128].

Very few studies have investigated the effects of Parkinson's disease on OKN. **Rascol et al** [138] found horizontal OKN responses were reduced in 45 subjects suffering from Parkinson's disease using EOG recording techniques. A finding supported by **Nakamura et al** [142] who also found reduced horizontal OKN responses in 11 out of 24 subjects with Parkinson's disease. More recently **Garbutt et al** [143] found no difference in the fast and slow OKN responses of five Parkinson's disease patients in both the horizontal and vertical directions when compared with a control group (figure 1.5). The target stimulus used in this investigation subtended 72°x60° with velocities ranging from 10 to 50°/s. The data was recorded using a magnetic search coil technique.

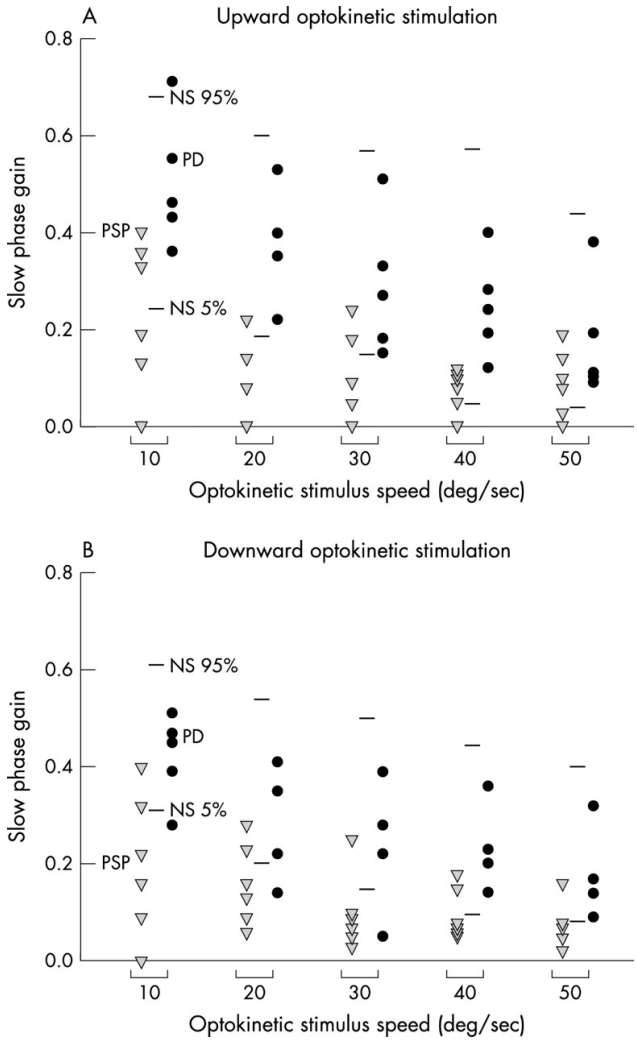


Figure 1.5: *Summary of mean slow phase gain (eye velocity/stimulus velocity) for individual patients with Parkinson's disease (PD) and progressive supranuclear palsy (PSP) for each stimulus used. (A) Responses to upward stimuli; (B) responses to downward stimuli. The horizontal lines indicate the 95% prediction intervals for normal subjects. In general, the patients with PSP showed lower gain values than did the controls, whereas those with PD showed responses similar to controls (see text for statistical comparisons). Closed circles, patients with PD; shaded triangles, patients with PSP. Reproduced from 'Abnormalities of optokinetic nystagmus in progressive supranuclear palsy' Garbutt S et al, Journal of Neurology, Neurosurgery & Psychiatry, 2004: 1386-94*

1.4 Recording Techniques and Test Stimuli

Various recording techniques have been used to record OKN responses in the literature. The earliest studies tended to use electro-oculography (EOG), a method which relies in the fact that the eyes have a resting potential generated by the retinal pigment epithelium. This can be detected by two small electrodes placed on the eyelids (figure 1.6). When the eyes move the electrical potential detected by the electrodes alter, one becoming more positively charged and the other more negatively charged. This change in electrical potential can be recorded and used to measure OKN responses.

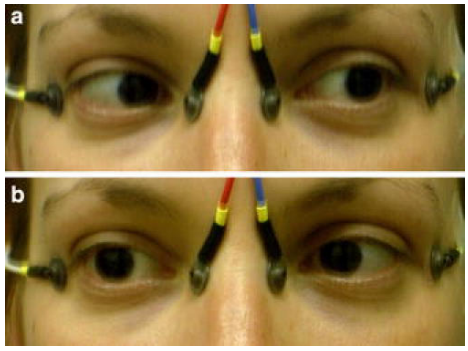


Figure 1.6: *Horizontal EOG electrode placement. Reproduced from 'ISCEV Standard for Clinical Electro-oculography (EOG) 2006' Brown M et al, Documenta Ophthalmologica, 2006: 205-12*

Magnetic search coils are a more modern and accurate eye movement recording technique. An observer wears a scleral contact lens with an electrode embedded in it (figure 1.6) whilst sitting in a strong magnetic field. When the eyes move a small electrical current is generated which can be recorded and used to assess OKN responses.

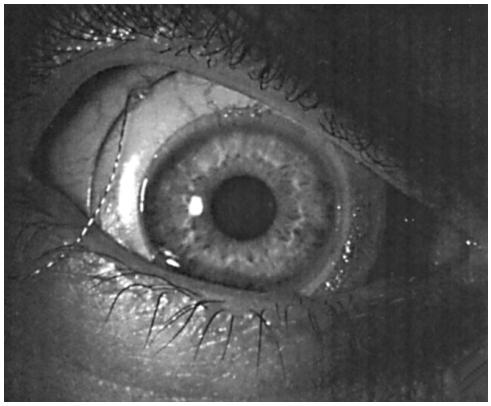


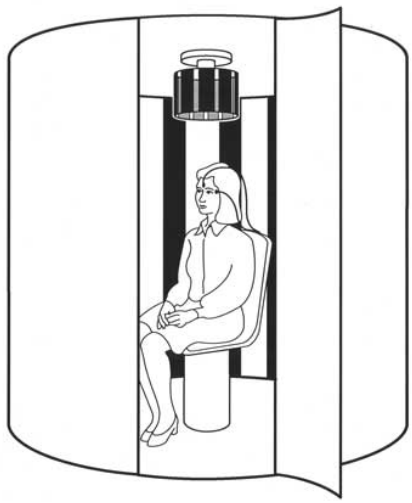
Figure 1.7: *Sclera search coil on the eye. Reproduced from: 'The effect of scleral search coil lens wear on the eye' Murphy PJ et al, British Journal of Ophthalmology, 2001: 332-5*

Another modern way to record eye movements is to use infra-red cameras to detect and track pupil movements. One of the main benefits of this system is that the instrument does not need to be in contact with either the eye or eyelids, making the technique more comfortable for the experimental subject. The system suspends two infra-red cameras front of both eyes and records infra-red images of the pupils (described in section 2, 'methods common to all investigations'). In this way eye movements can be detected and recorded.

A wide variety of test stimuli have been used to investigate OKN varying in size, contrast and type. Before the advent of sophisticated computers test targets typically consisted of a rotating black and white stripped OKN drum which was either hand held (figure 1.8) or projected on to the inside of a specially designed circular screen (figure 1.9).

Figure 1.8: *A hand held OKN drum*

Figure 1.9: *An OKN target projected on to a circular screen*



With development of computers, a wide range of OKN stimuli could be produced conveniently on a computer monitor or projected on to a tangent screen. The contrast luminance and speed of these targets can be tightly controlled and more complex stimuli including second order motion stimuli can be produced enabling horizontal, vertical and torsional OKN responses to be investigated under a wider range of experimental conditions

1.5 Summary

OKN is a reflex eye movement induced by motion of the whole or a large proportion of the visual field. It consists of two basic components, a slow tracking movement and a rapid recovery saccade.

The four nuclei implicated in the generation of OKN are the dorsal (DTN), lateral (LTN) and medial (MTN) terminal nuclei, which are collectively known as the accessory optic system (AOS), and the nucleus of the optic tract (NOT).

There is strong evidence in the literature to suggest that horizontal OKN is symmetrical in normal healthy adults and that horizontal OKN gains can be influenced by a variety of factors including target size, shape, contrast and velocity. The central retinal appears to be the most sensitive area of the retina for OKN generation and that in the presence of a central scotoma OKN gains tend to be reduced. Gravity also seems to have an affect on OKN symmetry, which suggests the vestibular system also exerts an influence over OKN. There is no evidence that OKN responses are affected by refractive error [144].

In early infancy before binocular vision has had time to develop, a physiological horizontal OKN asymmetry exists with a nasal preference. If binocular development is interrupted at this stage the asymmetry persists into adulthood. This would suggest that binocularity and its underlying cortical and subcortical processes are associated with the development of symmetrical horizontal OKN responses.

The nature of vertical OKN is less clear since the literature is inconsistent, making it difficult to determine whether an asymmetry exists in normal healthy adults and if one exists, the direction of the asymmetry. Of the studies published five suggest a vertical OKN asymmetry exists with a downward asymmetry, seven find an upward asymmetry and three find no asymmetry at all (see table 1.1).

The effects of Parkinson's disease OKN are also unclear. The most recent literature suggests there is no difference in the horizontal and vertical OKN responses in Parkinson's disease when compared with healthy subjects, whereas older publications suggest horizontal OKN responses are reduced.

1.6 Aims

There is a growing belief in the scientific community that vertical OKN is asymmetrical with an upward preference. However, during the pilot stages of a study to investigate the effects of neurological disease on OKN asymmetry, no vertical or horizontal OKN asymmetry was identified. This was totally unexpected. The first thoughts were that mistakes had been made during the analysis of the data. All data was re-analyzed with the Spike2 program using both automatic and manual techniques (see section 2.5 'data analysis') to ensure the analysis was as accurate as possible. No vertical asymmetry was identified.

Once experimental and analytical error was excluded, we needed to understand why our results differed from the accepted norm. An extensive literature search was performed to identify all of the research regarding vertical OKN. Having done this it became clear that vertical OKN had been investigated using a wide variety of target stimuli, recording techniques and working distances. It was also clear that some studies had examined very few subjects.

To investigate effects of neurological disease on vertical OKN asymmetry it is important to understand vertical OKN asymmetry in normal healthy adults.

The aim of our study was therefore to investigate vertical OKN asymmetry in healthy individuals under of variety of different experimental conditions and to compare the influence of these factors on vertical OKN asymmetry. Our hypothesis was that there was no evidence of a vertical OKN asymmetry in normal healthy adult subjects.

The investigations included: (i) the performance of look versus stare OKN, the effects of (ii) stimulus velocity, (iii) luminance profile, (iv) stimulus size and shape, and (v) distance on vertical OKN responses.

Repeated measures experimental designs were used to investigate the consistency of OKN asymmetries in individuals in comparison with the relative effects of these factors.

Only once vertical OKN asymmetry had been fully investigated could the effects of neurological disease on 'stare' OKN asymmetry be investigated. Parkinson's disease was chosen because it is a common neurological disorder with a consistent and specific underlying pathology. It is known to be associated with horizontal and vertical

oculomotor defects including deficits in saccadic eye movements and smooth pursuit. From what is known in the literature about the effects of Parkinson's disease on vertical OKN we hypothesized that the OKN responses would be symmetrical with reduced slow phase gains.

Unfortunately due to time constraints, we were unable to investigate the effects of Parkinson's disease on 'look' OKN responses.

1.7 Experimental Objectives

1.7.1 To investigate horizontal and vertical look and stare OKN symmetry in healthy adult volunteers

- To compare horizontal and vertical look and stare OKN asymmetry
- To compare each individuals' OKN asymmetry with the group as a whole and with the other individuals

1.7.2 The effects of different target characteristics on stare OKN asymmetry

- To assess the sensitivity of look and stare OKN to a variety of different stimulus parameters

1.7.3 To investigate the effects of viewing distance on OKN asymmetry

- To assess the effects of distance on OKN vertical asymmetry
- To assess the relationship between horizontal and vertical OKN

1.7.4 To investigate vertical stare OKN in Parkinson's disease

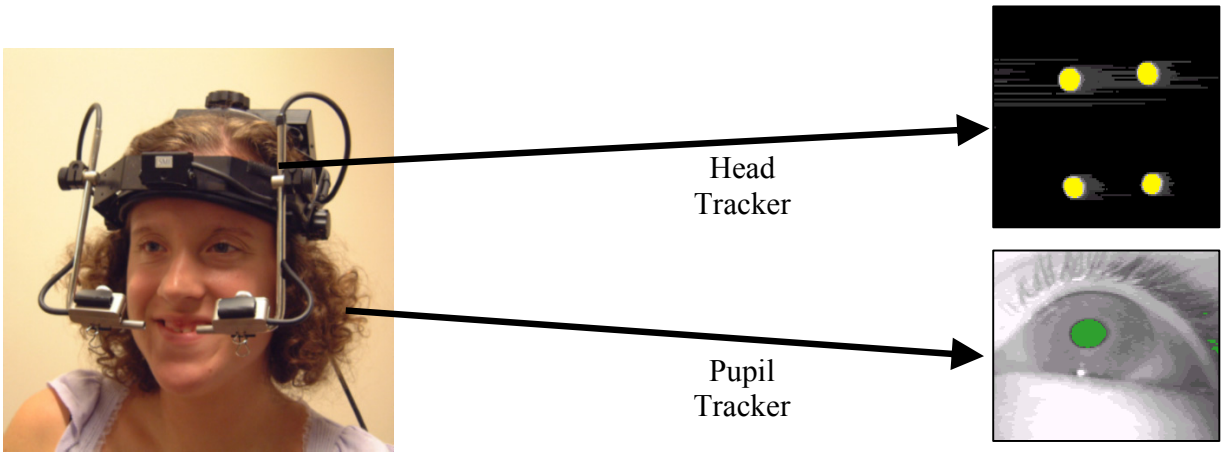
- To determine whether Parkinson's disease is associated with a vertical OKN asymmetry
- To assess whether vertical OKN gains are affected in Parkinson's disease
- To determine whether the severity of the Parkinson's disease has an effect on OKN

2. Methods Common to All Investigations

2.1 EyeLink I

All eye movement recordings in this series of investigations were made using the EyeLink I (SensoMotoric Instruments, GmbH, Berlin, Germany) high-resolution infrared video pupil tracker (sample rate 250Hz). It has a resolution of 0.005° and a noise level of < 0.01° RMS within a range of ± 30° (company specifications). The eye tracking range for pupils is ±30° horizontal and ±20° vertical. The image processing system uses a hybrid digital analogue technique and is compatible with most contact lenses and spectacles. It weighs approximately 600g in total (figure 1).

Figure 2.1: *A volunteer modeling the EyeLink I infra-red pupil tracker. Infra-red video cameras can be seen suspended from the head set below each eye. To the right are shown the infra-red pictures produced by the cameras. The upper picture shows the image produced by the head tracker enabling head movement to be detected. The lower picture shows the pictures produced by the two eye trackers suspended in front of each eye.*



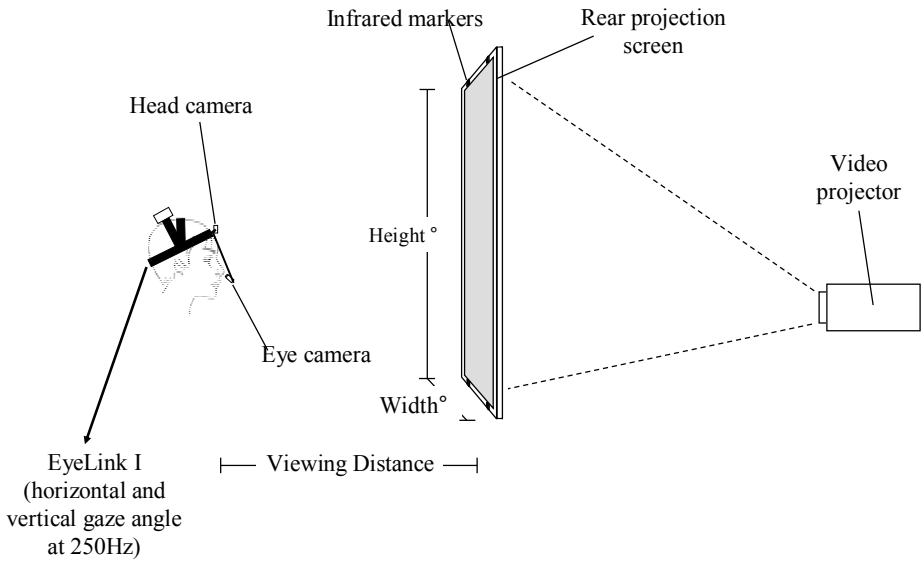
The tracker consisted of a two infra-red video cameras suspended from a headband (figure 2.1) enabling eye movement recordings to be made of both the right and left eyes during each study. Each camera is independently adjustable on the headband and before each set of recordings the cameras were positioned so that they did not impinge on the visual field of the observer, but allowed accurate recording of the eye movements. Where monocular recordings were being made the fellow eye was occluded by a

60x90mm square of black card mounted in front of the camera, preventing the eye from seeing the OKN target, but still allowing the eye to be monitored.

Before each study the pupil tracker was calibrated by asking each subject to fix on 9 points, projected in a 3 x 3 grid on to the target screen (figure 2). The calibration was repeated until the error between two measurements at any point was less than 1°, or the average error for all points was less than 0.5°. A drift correction was also performed prior to each trial.

For each investigation the observer sat in front either a rear projection tangent screen (figure 2.2) or a cathode ray tube (CRT) on which the target stimulus was produced. To minimize head movements and the introduction of artifact the observer placed his/her chin on a chin rest.

Figure 2.2: *Experimental set up demonstrating the experimental subject wearing the EyeLink I infra-red pupil tracker whilst seated before a rear projected tangent screen (nb a CRT computer monitor was used instead of the projection target in some tests)*



2.2 Computer control of EyeLink 1

Two personal computers are used to control EyeLink 1 and record the data;

- The first computer (the host PC) samples and processes the infra-red camera data and uses this information to determine the pupil and the head positions during each series of recordings. The software runs in MS-DOS to allow accurate timing (not permitted by Windows).
- The second computer (the display PC) sends commands to the first computer to initiate and manage the eye movement recordings. The display PC also controls two pieces of hardware for displaying visual stimuli (i) VisLab (Sensomotoric instruments GmbH, Berlin) which produces stimuli to calibrate eye movement data and perform a drift correction, and (ii) a VSG2/5 video card (Cambridge Research Systems, Rochester, UK). This is a high-resolution graphics video card capable of producing sophisticated moving stimuli with precise control over spatial and temporal stimulus frequencies.

The eye movement recordings are then converted offline to Spike 2 neurophysiological software system files (Cambridge Electronic Design, UK) for subsequent analysis.

2.3 VisLab

The 9 points used to calibrate the EyeLink pupil tracker before each series of eye movement recordings were produced by the VisLab projection system (Sensomotoric instruments, GmbH). This program runs in MS-DOS and is also responsible for generating the visual stimuli used in the fourth series of experiments (Vertical Optokinetic Nystagmus in Parkinson's Disease).

2.4 Generation of stimulus

The OKN target stimulus used in the first three eye movement investigations ('horizontal and vertical look and stare optokinetic nystagmus symmetry in healthy adult volunteers', 'the effects of target characteristics on OKN asymmetry' and 'the effect of distance upon horizontal and vertical look and stare OKN') were generated by the programmable VSG2/5 Visual Stimulus Generator video card (Cambridge Research

Systems, Rochester, UK). It was designed specifically for vision science applications and has an output resolution of 15 bits per colour channel for high resolution contrast and colour control. The VSG2/5 card requires Window as an operating platform. It is able to run independently from its host computer, such that once a stimulus is generated the card needs little intervention, leaving the computer to control the experiment and collect data.

2.5 Data Analysis

Once each series of tests were complete the movement recording data was converted to Spike 2 neurophysiological software system files (Cambridge Electronic Design, UK) before under going analysis.

The converted data was calibrated using the calibration files recorded before each test. This ensured that angle of deviation the eyes made during each test irrespective of the experimental working distance were consistent and therefore comparable. Once calibrated, the files were analysed using a Spike2 program custom written by a collaborator (Frank Proudlock - figure 2.3). The program calculated the total distance traveled during the slow tracking phase of the OKN response and divided it by the total duration of the slow phase response, allowing the mean slow phase velocity to be calculated. Slow phase gain was calculated from the ratio of mean slow phase velocity (MSPV) to the stimulus velocity of the target stimulus. This gives a weighted average of OKN gain which gives greater credence to longer slow phases.

To ensure the OKN data was analysed as carefully and accurately as possible a single observer examined each and every OKN trace. This process required the investigator to identify all of the OKN responses in the data recorded and mark the start and finish of each slow phase using a computer mouse. In this way eyelid blinks and other anomalous data could be identified and ignored. This process was essential since eyelid twitches could be easily misinterpreted as resetting saccades especially in subjects with dark eyelashes. Overall the process took approximately 45 minutes for each series of tests per subject, depending upon the nature of the experiment being carried out.

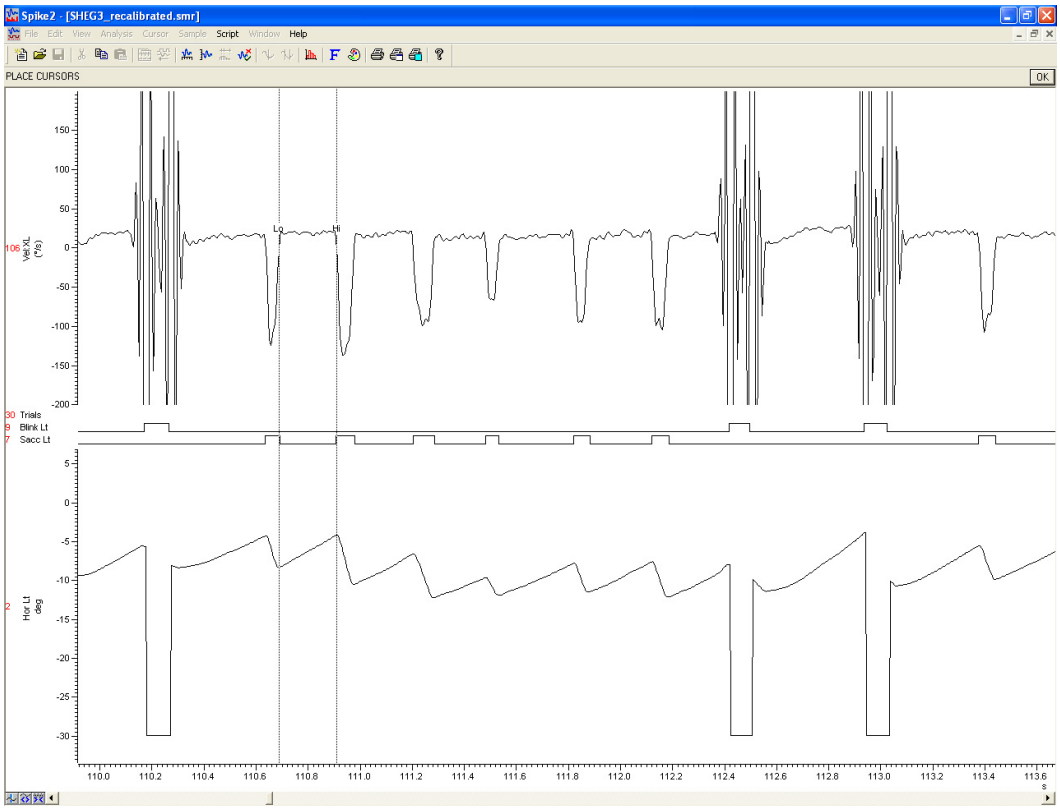


Figure 2.3: *An example of horizontal stare OKN data during analysis with the Spike2 program. The upper trace, the velocity channel (°/s), reveals a constant velocity during the slow 'pursuit' OKN movements interspersed with rapid velocity changes associated with OKN resetting saccades and eyelid blinks. The two traces below the velocity channel indicate when the subject blinks (the upper trace) whilst the lower one indicates a resetting saccade. The bottom trace shows the actual OKN response in either the horizontal or vertical plane (horizontal in this case), whilst along the 'x' axis the time duration is calibrated in seconds. The two vertical cursors are placed at the beginning and the end of the OKN slow phase response and the distance travelled between these points is measured. The sum of these distances is divided by the total duration of the slow phase response during the test to calculate the mean slow phase velocity. When performing the analysis automatically the computer uses the saccade channel to place the cursors at the beginning and end of the OKN slow phase response. During manual analysis the observer physically places the cursors at the beginning and end of each response.*

Once analysed using the Spike 2 program, the results were exported into a text file and subsequently imported into a Microsoft Excel template file where the mean slow phase velocity data each subject could be examined. This data was pooled with the results of other observers allowing OKN asymmetries to be assessed and be displayed graphically (example given in figure 2.4).

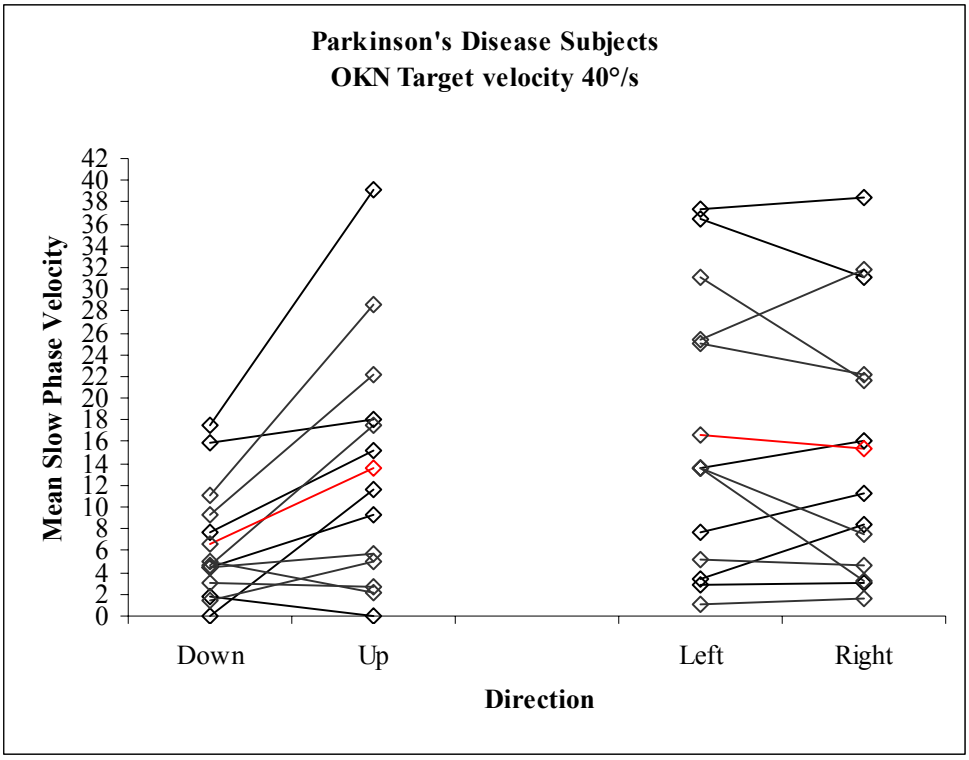


Figure 2.4: *A graph showing an example of OKN mean slow phase velocity responses. In this case 'stare' OKN of a group of Parkinson's disease subjects is shown observing a target with a velocity of 40°/s.*
The black lines link the horizontal and vertical OKN responses for each individual. The red line indicates the mean response for the group as a whole.

Asymmetry indices were calculated from the analysed data to identify any symmetry or asymmetry of the OKN responses for each individual, and when combined for the experimental groups as a whole. A value of 0.5 indicates there is no asymmetry, whereas a value of >0.5 indicates either an upward or nasal ward asymmetry, whilst a value of <0.5 indicates a downward or temporal ward asymmetry when using the following equations (MSPV = mean slow phase velocity):

$$\text{Vertical Asymmetry Index} = \frac{\text{Upward MSPV}}{\text{Upward MSPV} + \text{Downward MSPV}}$$

$$\text{Horizontal Asymmetry Index} = \frac{\text{Nasal ward MSPV}}{\text{Nasal ward MSPV} + \text{Temporal ward MSPV}}$$

3. Experimental Investigations

3.1 Investigation 1: Horizontal and Vertical Look and Stare Optokinetic Nystagmus Symmetry in Healthy Adult Volunteers

3.1.1 Introduction- Investigation 1

As previously mentioned in the general introduction, 'look' OKN and its asymmetry are poorly investigated in the literature when compared with 'stare' OKN. In addition, a direct comparison of 'look' and 'stare' OKN has not been investigated, either in terms of individual gains in nasal-ward, temporal-ward, upward and downward directions or in terms of horizontal and vertical asymmetries. The consistency of an individual's OKN asymmetry across a variety of different experimental conditions is unknown.

The aims of this investigation were to investigate horizontal and vertical asymmetries in 'look' and 'stare' OKN. To assess the consistency of each individuals' OKN asymmetry for both 'look' and 'stare' OKN, as well as comparing the monocular responses from the right and left eyes. The relationship between 'look' and 'stare' OKN responses in different directions of stimulus motion was also compared.

3.1.2 Methods- Investigation 1

Fifteen healthy volunteers (3 male, 12 female, age range 24-45 years, mean 32.4 years, SD ±5.8) were recruited. Both eyes were examined. There was no known history of any ophthalmic, neurological or otological abnormality. An orthoptic examination was performed on all volunteers to exclude amblyopia, binocular vision defects or any underlying ocular motility problems such as microstrabismus. No manifest strabismus was detected on performing a cover test. Table 3.1 summarizes the visual acuity, binocular vision and eye dominance each subject. All volunteers had a best corrected visual acuity of 0.0 logMAR (20/20) or better in each eye, with a difference of no more than 1 logMAR line between the two eyes. All volunteers achieved binocular vision of 60 seconds of arc or better using TNO test for stereoscopic vision (Richmond Products Inc,

Albuquerque NM). Contact lenses were used to obtain best correction when necessary to assist eye movement recordings (n=5).

Table 3.1: *Vertical / Horizontal asymmetry indices (see results section) compared with monocular visual acuity (on the LogMAR scale), stereoscopic vision measured using the TNO test, dominant (dom.) eye and whether the volunteer had a refractive error which needed correcting with contact lenses (CL).*

Experiment 1							
	Type of OKN		LogMAR VA				
Volunteer	Look	Stare	Left	Right	TNO	Dominant Eye	CL
Subject 1	0.49/0.53	0.42/0.49	-0.1	-0.1	15	Right	N
Subject 2	0.43/0.50	0.50/0.45	0.0	-0.1	60	Right	Y
Subject 3	0.45/0.50	0.44/0.54	-0.2	-0.2	15	Left	N
Subject 4	0.50/0.47	0.43/0.42	0.0	0.0	30	Left	N
Subject 5	0.64/0.54	0.59/0.54	-0.2	-0.2	30	Right	N
Subject 6	0.50/0.50	0.58/0.52	-0.1	-0.1	15	Right	Y
Subject 7	0.51/0.50	0.59/0.47	-0.1	-0.1	15	Right	Y
Subject 8	0.45/0.49	0.44/0.43	-0.2	-0.2	30	Right	N
Subject 9	0.47/0.51	0.55/0.38	-0.1	-0.1	15	Left	N
Subject 10	0.67/0.50	0.58/0.53	0.0	0.0	30	Right	N
Subject 11	0.39/0.49	0.20/0.61	0.0	0.0	30	Right	N
Subject 12	0.55/0.49	0.49/0.58	0.0	0.0	30	Right	N
Subject 13	0.62/0.51	0.69/0.49	-0.1	-0.1	15	Left	N
Subject 14	0.42/0.55	0.41/0.47	-0.1	-0.1	60	Right	Y
Subject 15	0.49/0.50	0.42/0.45	0.0	-0.1	60	Right	Y

OKN target stimuli were generated by a calibrated VSG2/5 card (described in the 'methods common to all investigations section') and presented on a CRT computer monitor (Nokia 446XS, screen size 365mm x 272mm) with an image resolution of 1024x768 pixels and frame rate 100Hz. The set-up was gamma-corrected using a photometer (OptiCAL, Cambridge Research Systems).

All eye movements were recorded using the EyeLink I high-resolution pupil tracker (described in the 'methods common to all investigations section') and then converted offline to Spike2 neurophysiological software system files for subsequent analysis.

The OKN stimulus was viewed monocularly at 330mm (resulting in a visual field of ±22.4° height and ±28.9° width). Head movements were kept to a minimum by stabilizing each test subjects' head on a chinrest, although the EyeLink eye tracker provides head compensated gaze data. The stimuli were presented for a period of 20 seconds and consisted of a sinusoidally modulated contrast grating (spatial frequency = 0.1 cycles/degree; Michelson contrast 50%; luminance from 13.37 to 39.89cdm^{-2}) moving at a linear velocity of 40°/s. All luminance readings were recorded using a radiometer (IL1700, R #106 radiance barrel, SEE038 detector, International Light, Newburyport, MS, USA) with a photopic filter that matches the CIE V(λ) photopic curve to within 1% total area error. The stimulus was shown moving in four directions: up, down, nasally and temporally with right eye viewing and left eye viewing. When measuring 'look' OKN, the subject was instructed to actively fix and follow individual OKN target stripes, whereas when examining 'stare' OKN, the subject was encouraged to look towards the centre of the screen whilst keeping the stripes in focus. All stimuli were presented in a random fashion and there was a gap of at least 15 seconds between each test stimulus.

The fast and slow phases of OKN were identified from eye movement recording data (figure 3.1) and the duration of individual slow phases was measured for all OKN responses. The distribution of the slow phase durations in the look and stare tasks were compared using histograms (figure 3.2). This provided the basis for identifying criteria to delineate between look and stare OKN responses, which was then applied to all of the OKN data analysed in the study (see results section for details).

Statistical analysis

Asymmetries were compared using the general linear model, with participants introduced as random factors (SPSS v11). Pearson's correlation was used to estimate consistency of gains between look and stare OKN and with either eye open.

3.1.3 Results

Delineating 'Look' and 'Stare' OKN

The eye movement traces recorded during the 'stare' OKN task were predominantly short duration slow phases with frequent quick phases (figure 3.1). The 'look' OKN data was more variable, consisting of two distinct waveforms, long duration slow phases with infrequent quick phases, and short duration slow phases with frequent quick phases. The short duration OKN cycles typically follow the large quick phase movements of look OKN, for all directions of stimulation, suggesting that this corresponded to the volunteers seeking the next stimulus stripe to follow. Thus the smaller amplitude cycles are more likely 'stare' OKN rather than 'look' OKN.

Figure 3.1: *Original data of look and stare OKN for stimuli moving in each direction from one individual (volunteer 3 right eye viewing). Movements in a temporalward or upward direction are indicated by an upward deflection of the trace and movements nasalward and downward by a downward deflection of the trace. Open arrows indicate the presence of stare OKN in the look OKN traces.*

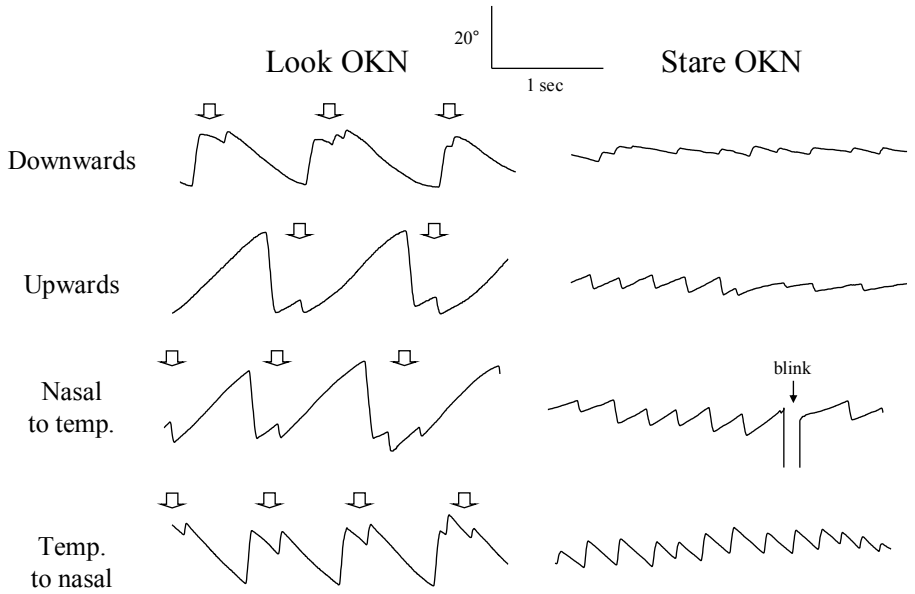


Figure 3.2 shows the distribution of slow phase durations during 'look' (2A) and 'stare' (2B) OKN trial. The 'look' OKN curve was bimodal consisting of a peak with its maximum at 0.25-0.3 sec and a second broader peak with its maximum at 0.85-0.9sec. The first peak represents "stare-like OKN" with cycles of short duration contaminating

the look data. The peak with its maximum at 0.25-0.3sec matches the maximum of the unimodal 'stare' OKN curve (figure 2B). To remove 'stare' OKN during the 'look' OKN trial only slow phases of duration > 0.45 seconds were included in the analysis, this representing the trough between the look and stare OKN peaks. The stare OKN trial was sub-analysed in a similar fashion for consistency to exclude any contamination with look OKN data.

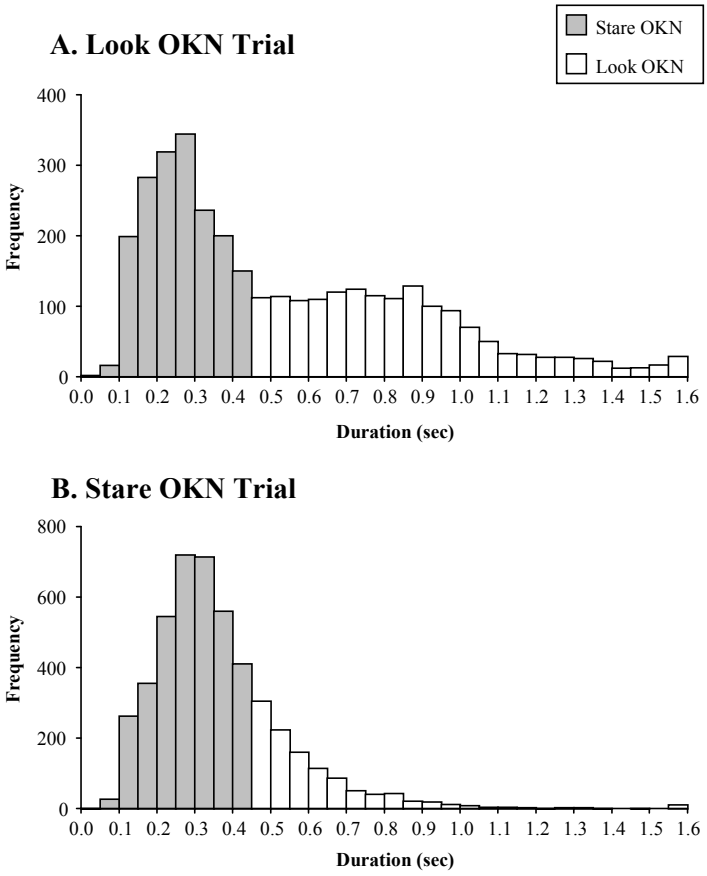


***Figure 3.2**: Histograms showing the distribution of duration of all slow phases from all volunteers during the (A) 'look' OKN trial, and (B) 'stare' OKN trial. Grey bars indicate data used in the analysis of stare OKN and empty bars in the analysis of look OKN.*

No horizontal or vertical OKN asymmetries (figure 3.3) were evident for either 'look' or 'stare' OKN when the sub-analysed data was compared (For 'look' OKN: F=0.03, p=0.86 for up versus down and F=2.7, p=0.12 for N>T (nasal to temporal) versus T>N (temporal to nasal) in the right eye, and F=0.33, p=0.57 for up versus down and F=0.50, p=0.50 for N>T versus T>N in the left eye. For 'stare' OKN: F=0.003, p=0.95 for up versus down and F=1.0, p=0.32 for N>T versus T>N in the right eye, and F=0.08, p=0.78 for up versus down and F=0.48, p=0.48 for N>T versus T>N in the left eye).

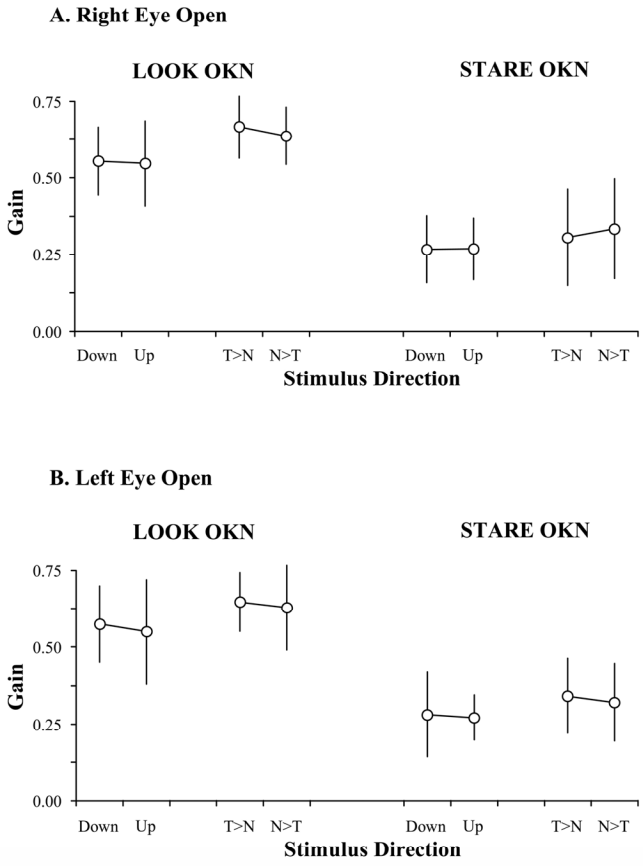
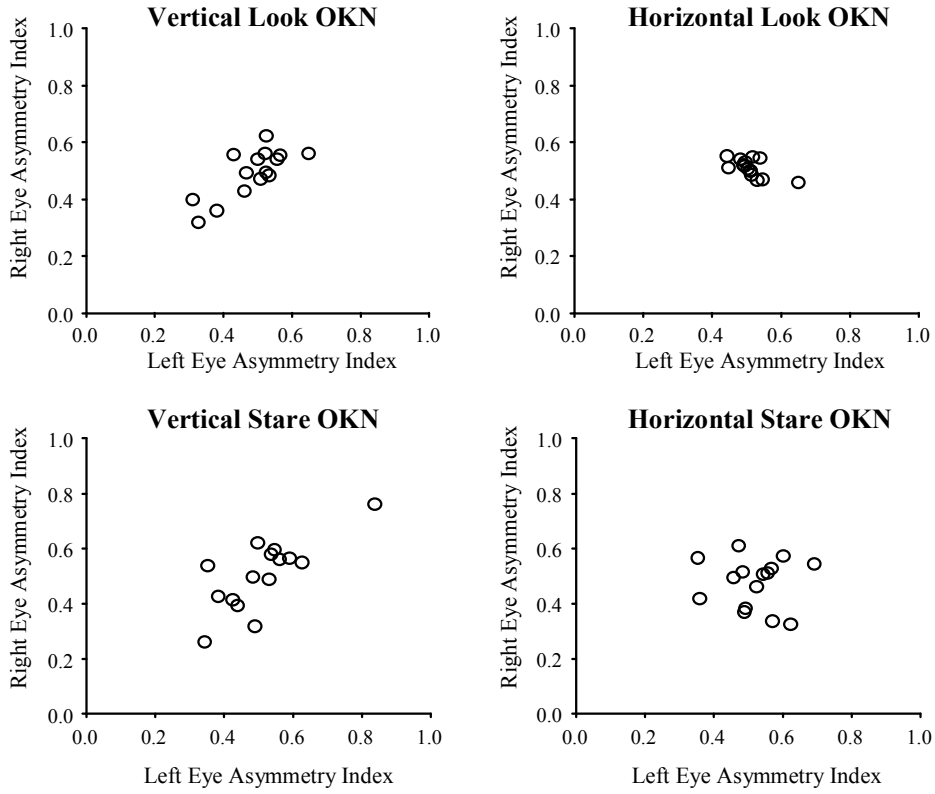


Figure 3.3: *Mean gains (±SD) for look and stare OKN in each stimulus direction comparing data for (A) right eye open with (B) left eye open. T>N indicates stimuli moving from temporal to nasal direction and N>T the opposite.*

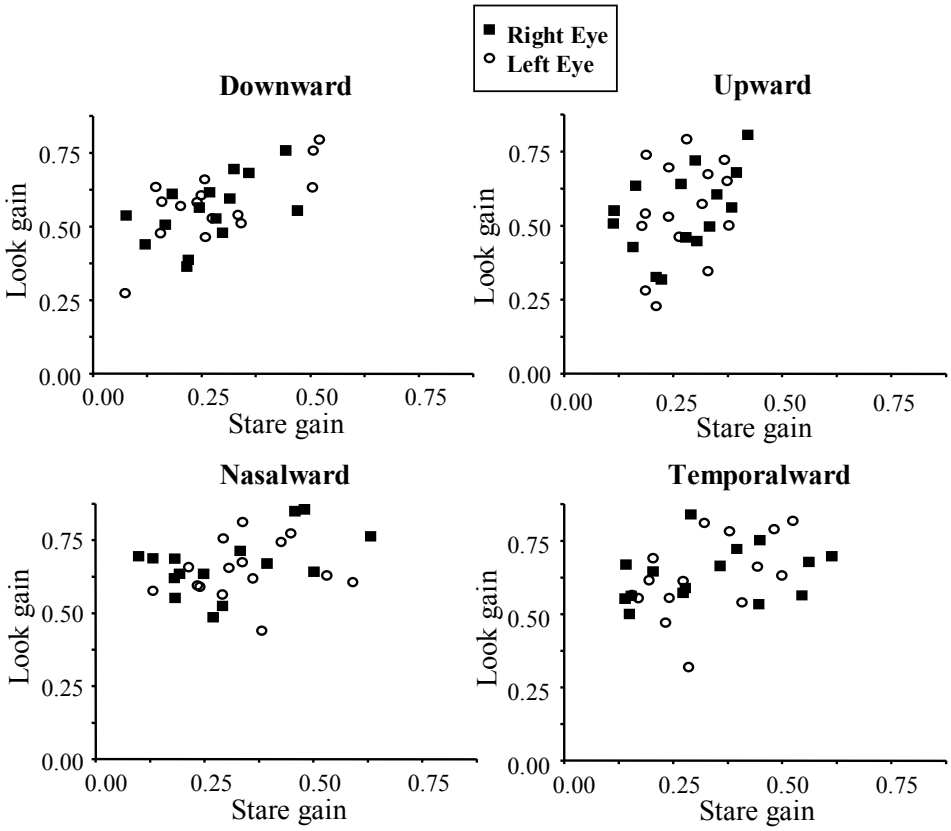
Although there was no overall vertical asymmetry, when the asymmetry indices for each individual were calculated for the right and left eyes, asymmetry indices showed a consistency when both eyes were compared with each other for vertical look OKN (r= 0.77, F=18.6, p=0.0008) and vertical 'stare' OKN (r= 0.75, F=16.9, p=0.001) (figure 3.4). There was less consistency for horizontal 'look' OKN (r=0.62, F=8.2, p=0.01) and no consistency between asymmetries for right and left eyes for horizontal stare OKN (r=0.06, F=0.05, p=0.82). Horizontal 'look' OKN was more symmetrical than either horizontal stare OKN or vertical 'look' and 'stare' OKN.

Figure 3.4: *Asymmetry indices for left eye plotted against right eye for each volunteer.*



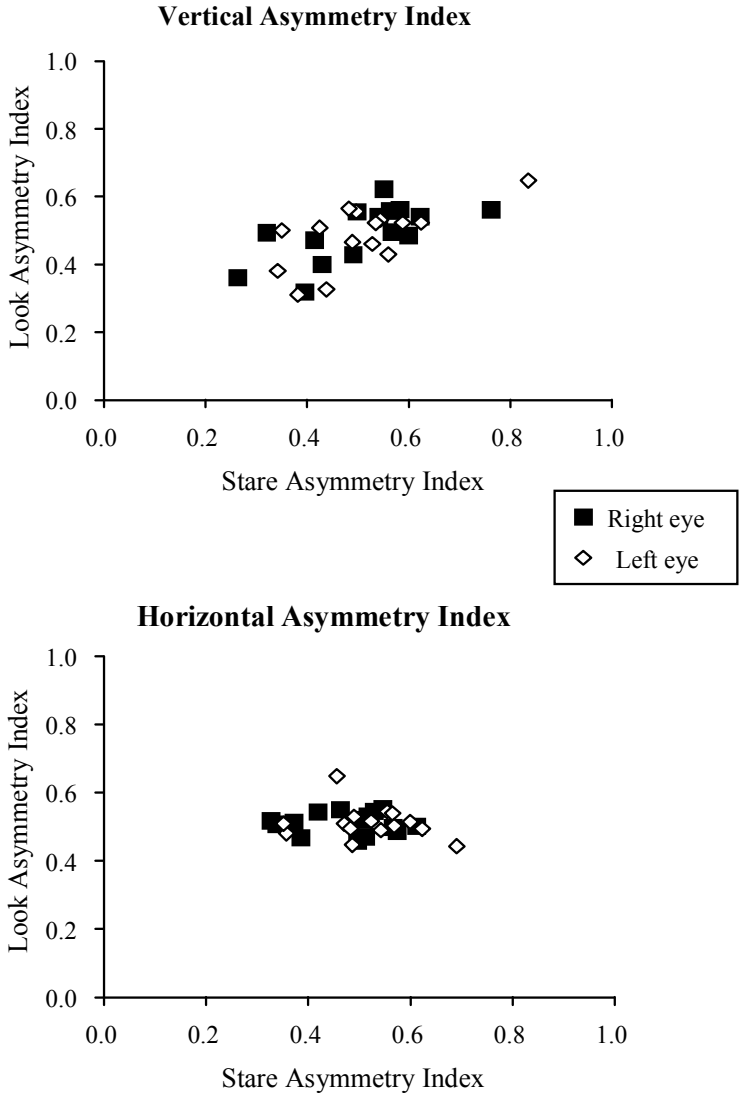
The mean gains for each individual were compared for 'look' and 'stare' OKN in figure 3.5 (means for left and right eyes averaged together for regression analysis). There was a stronger association when viewing a downward moving stimulus (r=0.73, F=14.5, p=0.002) than when viewing upward (r=0.41, F=2.6, p=0.13), nasal ward (r=0.44, F=3.3, p=0.09) or temporal ward (r=0.49, F=4.2, p=0.06) moving stimuli, where the associations were not significant.

Figure 3.5: *Plots showing the correlation between look and stare OKN mean gains for each individual and each eye in all four directions of stimulus motion.*



In addition there was a correlation between 'look' and 'stare' vertical OKN asymmetry indices (r=0.66, p=7.3x10^{-5}) calculated for each individual (means for left and right eyes averaged together). However, this was not the case for horizontal asymmetry indices of look and stare OKN (r=0.13, p=0.49) (figure 3.6). The line of the best fit for vertical asymmetry indices had a slope of 0.44 indicating that 'stare' OKN is more prone to vertical asymmetry than 'look' OKN (slope for horizontal asymmetry indices was 0.00).

Figure 3.6: *Correlation of asymmetry indices for look and stare OKN (filled squares = right eye, open diamonds = left eye).*



3.1.4 Discussion- Investigation 1

In this series of experiments we find no overall horizontal or vertical asymmetry in OKN gain for either 'look' or 'stare' OKN in the group of healthy young subjects. However, individuals tended to show a propensity for displaying a certain direction and degree of vertical asymmetry. This was evident from the consistency in vertical asymmetry seen when either left or right eye was viewing and when performing 'look' or 'stare' OKN (although degree of asymmetry was less for 'look' OKN). 'Look' and 'stare' OKN were most strongly correlated when tracking stimuli moving downwards. We also found that the 'look' OKN traces were often mixed with 'stare' OKN data which needed to be removed during the analysis to prevent erroneous results.

The novel finding in this study was the propensity individuals show for a certain direction and degree of vertical asymmetry rather than the vertical asymmetry of the group as a whole. This is most clearly seen from the strong correlation in vertical asymmetry index for individuals viewing with either right or left eye. Since vertical eye movements are conjugate, the comparison of left and right eyes viewing allows comparison of intra-subject versus inter-subject variability. This has not been investigated in earlier studies. The cause of the idiosyncratic nature of vertical OKN is unclear.

The consistency of vertical asymmetry indices was also observed between 'look' and 'stare' OKN responses. This was evident even though 'look' OKN is more vertically symmetrical than 'stare' OKN. The greater symmetry of 'look' OKN may be due to the larger gains observed for look OKN, which may in turn be because of the link between 'look' OKN and smooth pursuit which is well developed in humans. Interestingly, 'look' and 'stare' OKN is more strongly associated when following stimuli moving downwards compared to stimuli moving either upwards or even nasal ward or temporal ward. In the natural realm, OKN responses in humans are most commonly generated from global motion (called optic flow) caused by locomotion through space, i.e. walking and running in humans. During natural locomotion, downward motion is often the strongest stimulus due to the proximity of the ground.[145]

Our inability to find a horizontal asymmetry is not surprising since there is a general consensus that horizontal OKN is symmetrical in normal healthy individuals [98 102 106 107 109 116 146]. It is interesting to note that in our study we found certain individuals

displayed a propensity for a preference towards either temporal ward or nasal ward moving stimuli when horizontal ‘look’ OKN was investigated. This finding was consistent despite varying stimulus parameters used. However, horizontal ‘stare’ OKN asymmetry did not appear to be consistent (figure 3.4, bottom right graph) and suggests that idiosyncratic traits independent for either eye could be responsible for this.

3.2 Investigation 2: The Effects of Target Characteristics on Stare OKN Asymmetry

3.2.1 Introduction- Investigation 2

Over the years a wide variety of target stimuli have been used to investigate OKN. It is unclear whether any of these target parameters affects OKN asymmetry since they have never been directly compared with each other on the same group of subjects.
We investigated the effect of different stimulus parameters (velocity, contrast, type of grating, stimulus shape) on the horizontal and vertical asymmetries of 'stare' OKN, which was chosen due to time limitations and also because 'stare' responses are considered to be a 'pure' form of OKN. 'Look' OKN responses on the other hand are possibly a combination of 'stare' OKN and smooth pursuit (as discussed section 3.1.4 of the previous investigation).

3.2.2 Methods- Investigation 2

Nine healthy volunteers (1 male, 8 female, age range 24-45 years, mean 32.1 years, SD ±6.7) were recruited for this study. Only the right eye of each subject was investigated with the left eye occluded. Six subjects were emmetropic for distance, whilst the other three were fully corrected for distance with contact lenses. All had a best corrected visual acuity of 0.0 logMAR (20/20) or better in each eye, with a difference of no more than 1 logMAR line between each eye and good binocular vision of (60 seconds of arc or better). There was no known history of any ophthalmic, neurological or otological abnormality.

The OKN target stimuli were viewed at 330mm on a CRT (Nokia 446XS, screen size 365mm x 272mm) giving a visual field of ±22.4° height and ±28.9° width. The image resolution was 1024x768 pixels with a frame rate of 100Hz. A CRT was used in preference to an LCD projector to give greater resolution of luminance. All stimuli were produced by a VSG 2/5 high-resolution video card and the eye movements were recorded using the EyeLink I pupil tracker (as described earlier in the 'methods common to all investigations section')

In this investigation only the right eye of each subject was examined. This was achieved by mounting a square black occluder (60x90mm) in front of the left eye and camera. Once again head movements were minimised using a chinrest.

'Stare' OKN responses were investigated in four directions of gaze under a variety of stimulus parameters:

(i) Velocity (20°/s and 40°/s)

(ii) Contrast (50% and 100% where luminance was from 13.37 to 39.89 cdm^{-2} for 50% contrast and from 0.10 to 53.16 cdm^{-2} for 100% contrast)

(iii) Grating luminance modulation (sine wave and square modulated contrast). All combinations of these three parameters were tested using a stimulus covering the full extent of the CRT screen.

(iv) In addition, the two stimulus velocities and contrasts were also tested, using a circular vignetted stimulus (diameter ±22.4°, background luminance = 11.60 cdm^{-2}) but only using the sine wave modulated grating.

All luminance readings for this experiment were recorded using a radiometer (IL1700, R #106 radiance barrel, SEE038 detector, International Light, Newburyport, MS, USA) with a photopic filter that matches the CIE V(λ) photopic curve to within 1% total area error.

Statistical analysis

A linear mixed model was used with either OKN gain or asymmetry index as the dependent variable and including all the parameters as fixed factors to investigate the most potent effects on OKN asymmetries. Coefficients of variation (%) were calculated to estimate both the between and within subject variability.

3.2.3 Results- Investigation 2

The 'stare' OKN data was sub-analysed to filter out erroneous 'look' OKN data (see 3.1.3 the results section of investigation 1: 'horizontal and vertical look and stare optokinetic nystagmus symmetry in healthy adult volunteers) to ensure a consistency of the data. Analysis of the fixed factors introduced into the general linear model showed that stimulus velocity had a large effect on OKN gain in all four directions of gaze

(*F*=122.8, *p*<0.001 for downward; *F*=124.8, *p*<0.001 for upward; *F*=20.6, *p*<0.0001 for nasal ward and *F*=26.2, *p*<0.0001 for temporal ward). Grating contrast had a significant effect mainly on vertical OKN gain (*F*=4.07, *p*=0.05 for downward; *F*=6.21, *p*=0.01 for upward; *F*=1.73, *p*=0.19 for nasal ward and *F*>0.001, *p*=0.98 for temporal ward), whilst grating luminance modulation had a small effect on upward OKN gain (*F*=0.53, *p*=0.47 for downward; *F*=4.68, *p*=0.03 for upward; *F*=0.96, *p*=0.33 for nasal ward and *F*=0.04, *p*=0.84 for temporal ward). The use of the circular vignetted stimulus resulted in significantly smaller gains than using the whole screen with the effect much more obvious for vertical OKN than for horizontal OKN (*F*=24.4, *p*<0.0001 for downward; *F*=20.8, *p*<0.0001 for upward; *F*=6.65, *p*=0.01 for nasal ward and *F*=5.15, *p*=0.03 for temporal ward).

Table 3.2: *Vertical / Horizontal asymmetry indices compared with monocular visual acuity (on the LogMAR scale), stereoscopic vision measured using the TNO test, dominant (dom.) eye and whether the volunteer had a refractive error which needed correcting with contact lenses (CL).*

Contrast	**50%**										
Grating	**square**				**sine**						
Field	**full**		**circle**		**full**		**LogMAR VA**				
Stim. velocity	20°/s	40°/s	20°/s	40°/s	20°/s	40°/s	Left	Right	TNO	Dom. eye	CL
Subject 1	0.61/0.52	0.64/0.43	0.53/0.58	0.58/0.46	0.53/0.52	0.52/0.56	-0.1	-0.1	15	Right	N
Subject 2	0.51/0.54	0.40/0.65	0.60/0.57	0.54/0.50	0.51/0.55	0.51/0.60	0.0	-0.1	60	Right	Y
Subject 3	0.54/0.47	0.52/0.49	0.62/0.53	0.47/0.49	0.46/0.51	0.42/0.47	-0.2	-0.2	15	Left	N
Subject 4	0.50/0.44	0.57/0.52	0.45/0.57	0.62/0.55	0.45/0.39	0.49/0.53	0.0	0.0	30	Left	N
Subject 5	0.44/0.51	0.50/0.56	0.37/0.47	0.44/0.49	0.44/0.55	0.53/0.47	-0.2	-0.2	30	Right	N
Subject 6	0.46/0.51	0.38/0.51	0.46/0.51	0.37/0.51	0.44/0.50	0.41/0.55	-0.1	-0.1	15	Right	Y
Subject 16	0.38/0.47	0.48/0.46	0.55/0.43	0.46/0.47	0.41/0.47	0.39/0.44	0.0	-0.1	30	Left	N
Subject17	0.43/0.42	0.54/0.38	0.50/0.45	0.41/0.51	0.52/0.43	0.57/0.30	-0.1	-0.1	60	Right	N
Subject 18	0.48/0.45	0.39/0.45	0.46/0.44	0.46/0.36	0.46/0.44	0.46/0.42	0.0	-0.1	30	Right	N

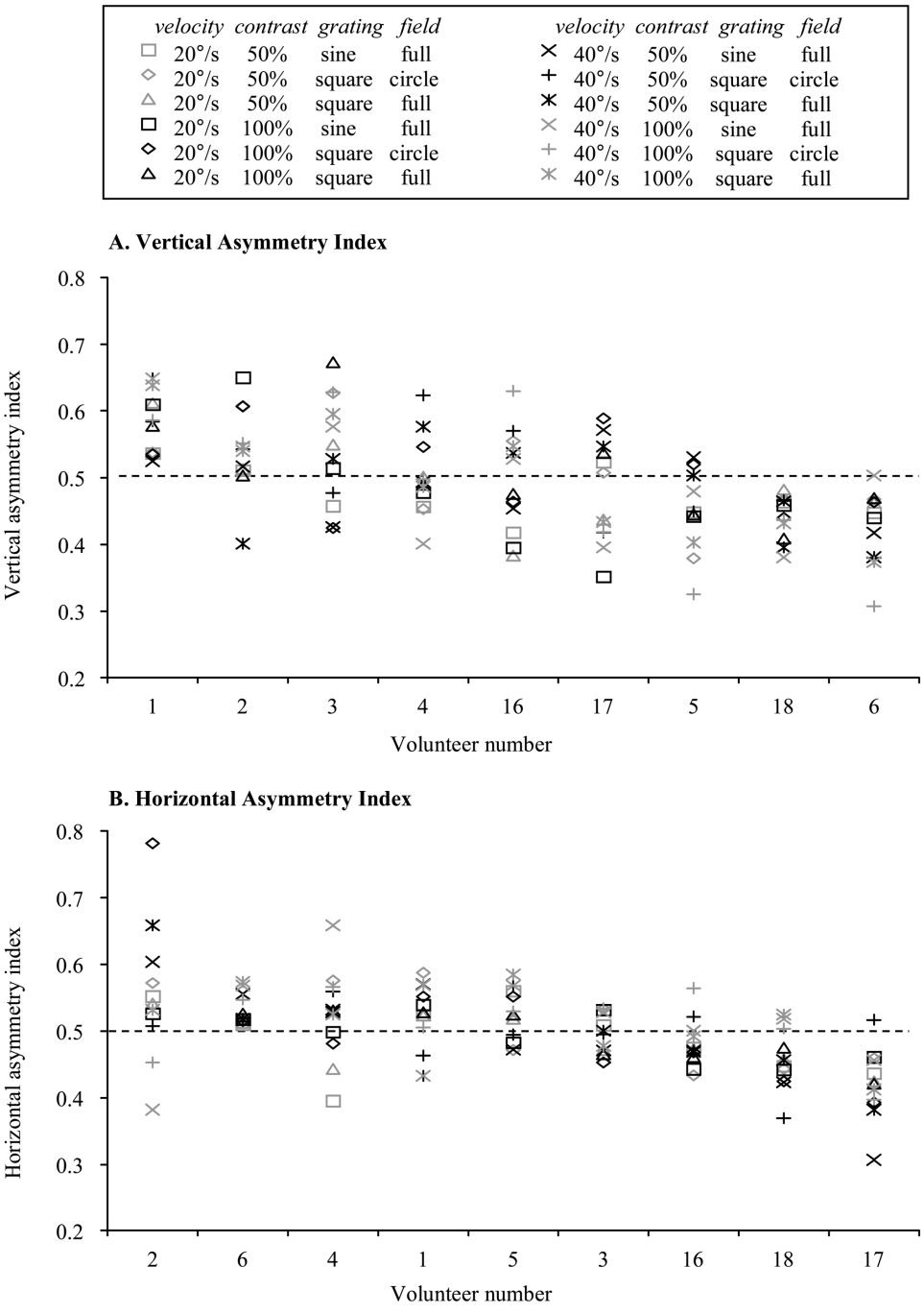
Contrast	**100%**										
Grating	**square**				**sine**						
Field	**full**		**circle**		**full**		**LogMAR VA**				
Stim. velocity	20°/s	40°/s	20°/s	40°/s	20°/s	40°/s	Left	Right	TNO	Dom. eye	CL
Subject 1	0.57/0.52	0.63/0.56	0.53/0.55	0.58/0.50	0.60/0.53	0.64/0.43	-0.1	-0.1	15	Right	N
Subject 2	0.50/0.83	0.54/0.53	0.60/0.78	0.55/0.45	0.64/0.52	0.54/0.38	0.0	-0.1	60	Right	Y
Subject 3	0.67/0.46	0.59/0.47	0.42/0.45	0.62/0.53	0.51/0.53	0.57/0.52	-0.2	-0.2	15	Left	N
Subject 4	0.48/0.53	0.48/0.52	0.54/0.48	0.49/0.56	0.47/0.49	0.40/0.65	0.0	0.0	30	Left	N
Subject 5	0.44/0.52	0.33/0.53	0.51/0.55	0.40/0.58	0.44/0.48	0.48/0.57	-0.2	-0.2	30	Right	N
Subject 6	0.46/0.52	0.37/0.57	0.46/0.51	0.30/0.54	0.43/0.51	0.50/0.56	-0.1	-0.1	15	Right	Y
Subject 16	0.47/0.46	0.54/0.49	0.46/0.46	0.62/0.56	0.39/0.44	0.52/0.49	0.0	-0.1	30	Left	N
Subject17	0.53/0.42	0.43/0.41	0.58/0.39	0.41/0.39	0.35/0.46	0.39/0.45	-0.1	-0.1	60	Right	N
Subject 18	0.40/0.47	0.43/0.52	0.43/0.42	0.43/0.50	0.45/0.44	0.38/0.51	0.0	-0.1	30	Right	N

None of the parameters had any significant effect on either the horizontal asymmetry indices (F=0.002, p=0.96 for velocity; F=2.00, p=0.16 for contrast; F=0.76, p=0.38 for grating modulation and F=0.02, p=0.89 for field shape) or the vertical asymmetry indices (F=0.02, p=0.87 for velocity; F=0.41, p=0.52 for contrast; F=0.81, p=0.37 for grating modulation and F=0.14, p=0.70 for field shape) (see table 3.2).

Given the large number of different stimulus parameters we might predict high within-subject variation of OKN gain when compared with between-subject variation, however, within-subject and between-subject variation were similar in magnitude. Within-subject coefficients of variation were 22.1%, 22.1%, 21.9%, 21.7% for upwards, downward, nasal and temporal directions, respectively. Between-subject variation was similar but slightly higher than with-in subject variation for downward, nasal and temporal OKN gains (coefficients of variation were 26.8%, 27.8% and 29.8%, respectively), but lower for upward OKN gain (coefficient of variation was 16.9%). Likewise, between-subject variation for asymmetry indices was still relatively high at 70-80% of within subject variation (vertical asymmetry index: within = 12.8%, between = 9.8%, and horizontal asymmetry index: within = 12.3%, between = 8.5%).

The relatively high between-subject variation can be seen in figure 3.7, where asymmetry indices for all combinations of stimuli are grouped for each volunteer (arranged in order of mean asymmetry index). The figure illustrates that vertical and horizontal asymmetries are often consistent in a certain individual even using a variety of stimulus designs. For example, the volunteers on the left of the graph tended to show asymmetry indices above 0.5 (i.e. upward>downward and nasal ward>temporal ward) for most trials whereas volunteers on the right of the graph tended to show asymmetry indices below 0.5 for most trials. This pattern was observed for both vertical and horizontal indices although the correlation between individual vertical and horizontal indices (means of all values) was not significant (p=0.06). The tendency for a horizontal or vertical asymmetry was not correlated with any differences in the visual acuity between the two eyes, eye dominance or stereoscopic vision (see table 3.2).

Figure 3.7: *Asymmetry indices for each combination of parameters (20°/s and 40°/s velocity, 50% and 100% contrast, sinusoidal and square wave modulated gratings, and full screen or circular vignetted field) grouped for each individual.*



3.2.4 Discussion- Investigation 2

OKN responses to vertically moving stimuli appear to be more sensitive to changes in stimulus parameters than horizontally moving stimuli. Target velocity seems to have the greatest effect on OKN gain in all directions, whilst grating contrast and the grating contrast profile seems to influence only vertical OKN gains. Interestingly the circular vignetted target resulted in reduced horizontal and vertical OKN gains, which was particularly noticeable vertically. This is striking since **Van Die et al** [117] found that a small 10° target elicited horizontal OKN responses similar to those resulting from full field stimulation (180° x 105°).

None of the parameters investigated had any significant effect on either vertical or horizontal OKN asymmetry, which was at variance with the findings by **Murasugi et al** [39] , who using a different experimental set up, found an upward vertical OKN asymmetry with a large screen stimulus (61° x 64°) and no asymmetry with a small central 10° x 6° OKN stimulus. The two targets used in our study, a rectangular stimulus ±22.4° x ±28.9° (44.8° x 57.8°) and a circular vignetted stimulus of ±22.4° (44.8°), had no effect on OKN asymmetry.

Interestingly, both the horizontal and vertical asymmetries observed in individual subjects were relatively consistent irrespective of the different stimulus parameter investigated.

It is unlikely that the differences in vertical OKN asymmetry reported in the literature are due to variations in target velocity, contrast or the grating luminance modulation (sine wave / square wave).

3.3 Investigation 3: Viewing Distance Study

3.3.1 Introduction- Investigation 3

The effect of different viewing distances and vergence on OKN responses is poorly understood. To our knowledge only one study by **Jagla et al** [147] has systematically explored the effect of distance on horizontal OKN. This found that OKN gain decreased for the shortest working distances. The effect of target distance on vertical OKN asymmetry has not been investigated. However it is known that the gain of the vestibulo-ocular reflex (VOR), which is closely related to OKN [39], depends upon the distance between an observer and visual target to maintain image stability on the retina during motion. The vergence angle is the most important factor to influence the change in VOR gain with distance [148 149]. It is possible that OKN responses may also be influenced by vergence angles.

It is clear from the literature that a wide range of different working distances have been used to investigate OKN asymmetry. It is possible that any asymmetry seen in these studies result from the proximity of an observer to the OKN target stimulus, and hence the effects of accommodation or vergence angles. We therefore explored the effect of distance on both horizontal and vertical 'look' and 'stare' OKN. Three different distances and two different stimulus sizes were compared (only one size could be used for the furthest distance due to constraints imposed by the equipment and laboratory size), matching stimulus parameters such as visual angles and contrast. Measurements at near were made with and without glasses to explore possible confounding affects of accommodation.

3.3.2 Methods- Investigation 3

Sixteen healthy volunteers (4 male, 12 female, mean age 31.4 years, SD 6.7 years) with no known history of ophthalmological, neurological or otological abnormality were recruited to the study. An orthoptic examination was performed on all volunteers to exclude amblyopia, binocular vision defects and any underlying ocular motility problems such as strabismus. All volunteers had a best corrected visual acuity of 0.0 logMAR or better in each eye (difference between eyes >=1 logMAR line) and achieved binocular

vision of 60 seconds of arc or better using TNO test for stereoscopic vision (Richmond Products Inc, Albuquerque NM). Contact lenses were used to obtain best correction when necessary to assist eye movement recordings (n=4).

The OKN test stimuli for all three test distances (0.33m, 1m and 2.5m) consisted of a sinusoidally modulated contrast grating (spatial frequency = 0.26 cycles/degree; peak to peak contrast 93%; luminance from 0.45 to12cdm^{-2}) moving at a linear velocity of 38.4°/s. All were projected onto a rear projection screen (1.75m width and 1.17m height) using an Epson EMP-703 (resolution 1024x768, frame rate 60Hz) driven by a calibrated high-resolution VSG 2/5 video card. The set-up was gamma-corrected using a photometer (OptiCAL, Cambridge Research Systems). Luminances were matched for different distances by varying the contrast and brightness on the projector. A radiometer (IL1700, R #106 radiance barrel, SEE038 detector, International Light, Newburyport, MS, USA) with a photopic filter that matches the CIE V(λ) photopic curve was used to match the luminances. The stimulus was shown moving in four directions: up, down, nasally, temporally. 'Look' and 'stare' OKN were recorded under the following conditions:

(i) A larger stimulus of ±40° width and ±30° height was tested at 0.33m and 1m distance.

(ii) A smaller stimulus of ±10° width and ±7.5° height was tested at 0.33m, 1m and 2.5m distance.

(iii) Both larger and smaller stimuli at 0.33m were tested with and without the addition of a near vision spectacle correction to compare the effects of near adaptation and accommodation on OKN.

Eye movements were recorded using the high-resolution EyeLink I pupil tracker (described earlier in the 'methods common to all investigations section'). To ensure the OKN stimulus was viewed monocularly an occluder was mounted on the camera in front of the non-viewing eye.

OKN stimuli were presented in random order at each test distance for a period of 20 seconds followed by a rest period of 15 seconds. This period was used to ensure that any OKAN (optokinetic after nystagmus), should it occur, would not interfere with the subsequent eye movement recordings.

When measuring 'look' OKN the subject was instructed to actively fix and follow individual OKN target stripes, whereas when examining 'stare' OKN, the subject was encouraged to look towards the centre of the screen and keep the OKN stripes in focus. 'Look' OKN was defined as having a slow phase of > 0.45 seconds duration and stare OKN as having a duration < 0.45 seconds. The justification for this is described in investigation 3.1 ('horizontal and vertical 'look' and 'stare' optokinetic nystagmus symmetry in healthy adult volunteers').

Statistical analysis

Linear mixed models were used to estimate the effects of distance and stimulus size on OKN gain and asymmetry index including interactions in the models (SPSS v11). Gains were transformed using natural logarithm to yield distributions that were more normally distributed. Coefficients of variation (%) were calculated to estimate both the between and within subject variability.

3.3.3 Results- Investigation 3

Original recordings from a representative subject are shown in figure 3.8 for all experimental conditions. As previously described in investigation 3.1 ('horizontal and vertical 'look' and 'stare' optokinetic nystagmus symmetry in healthy adult volunteers') the 'look' OKN traces are contaminated with 'stare' OKN responses.

Interestingly when the slow phase responses of 'look' OKN are observed, the amplitudes are greater with large field stimulation (80° x 60°) when compared with the small field stimulation (20° x 15°). Stare OKN is characterised by a typical saw-toothed waveform for all stimulus conditions.

The change in mean gain with distance is represented in figure 3.9 for large field and small field stimuli. Distance had no significant effect on 'look' OKN gains (rightward: F=0.54, p=0.59; leftward: F=0.16, p=0.85; upward: F=1.25, p=0.29; downward: F=1.15, p=0.32). However 'stare' OKN gains were affected by distance. An increasing target distance significantly reduced stare OKN gains when subjects viewed a target stimulus moving in a downwards direction (rightward: F=1.64, p=0.20; leftward:

F=1.35, p=0.27; upward: F=1.97, p=0.15; downward: F=6.68, p=0.002). Overall, however there was no significant vertical stare OKN asymmetry.

In contrast to distance, stimulus size had a considerable effect on 'look' and 'stare' OKN gains in all directions with a greater effect on the vertical optokinetic response and especially the upward response (look OKN: rightward: F=9.5, p=0.003; leftward: F=15.8, p=0.0001; upward: F=69.6, p=1x10^{-11}; downward: F=43.6, p=2x10^{-8}; stare OKN: rightward: F=7.7, p=0.007; leftward: F=3.85, p=0.05; upward: F=84.2, p=5x10^{-13}; downward: F=27.9, p=2x10^{-6}). The smaller target stimulus (20°x15°) resulted in lower OKN gains when compared with the larger stimulus size (80°x60°). A greater sensitivity of the vertical OKN system to stimulus size resulted in a larger difference between horizontal and vertical OKN responses when viewing the smaller stimulus. This was particularly noticeable with the look OKN responses.

Figure 3.8: *Original recordings from the right eye of one representative volunteer for all stimulus conditions tested.*

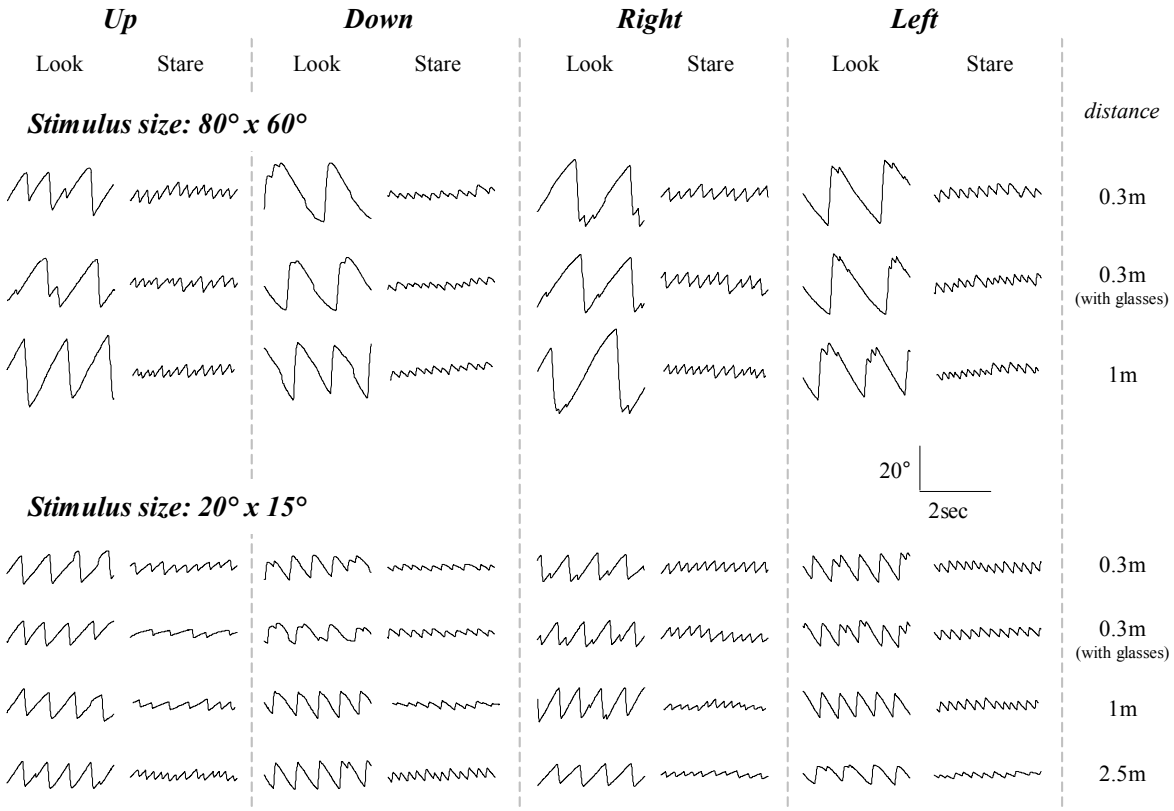
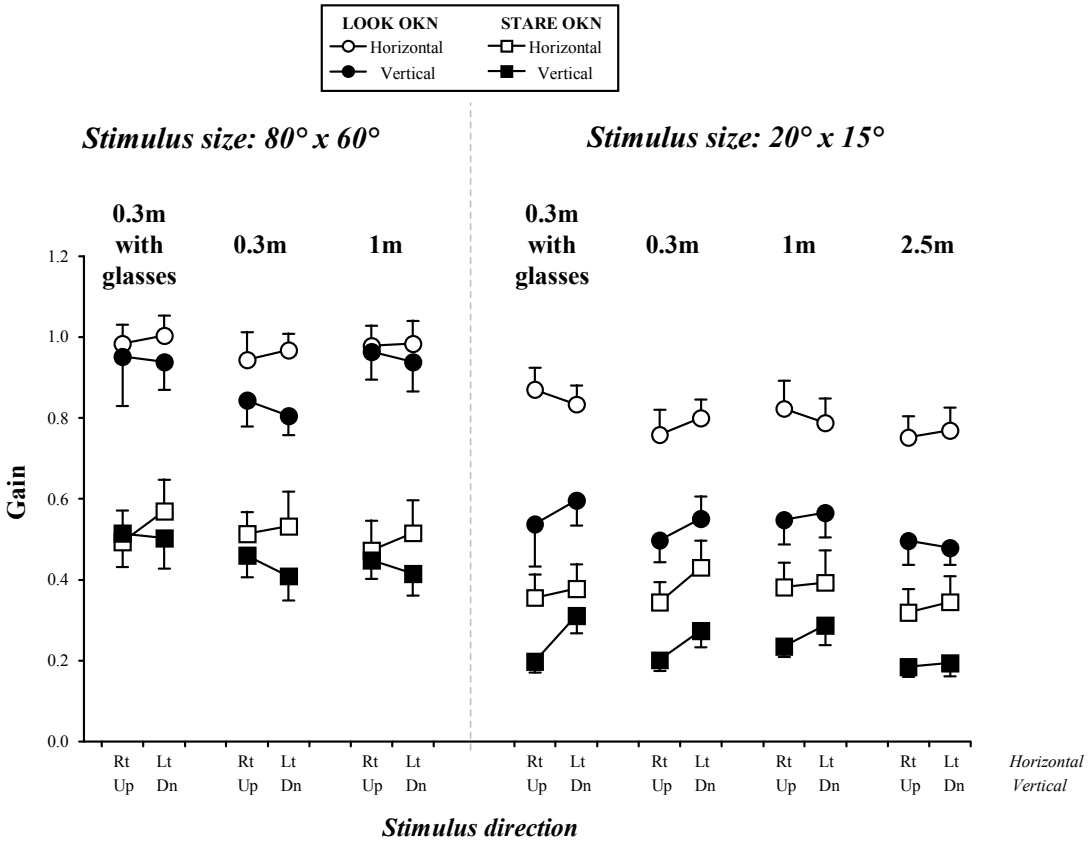


Figure 3.9: *Mean OKN gains for all stimulus conditions tested. Open symbols represent horizontal OKN and filled symbols vertical OKN. Look OKN is represented with circles and stare OKN with squares. Rt = rightward, Lt = leftward, Up = upward and Dn = downward for stimulus directions.*



Horizontal and vertical asymmetry indices for both look and stare OKN are shown in figure 3.10. Overall target distance has no significant effect on horizontal and vertical asymmetry with either 'look' OKN (horizontal asymmetry index: F=1.10, p=0.33; vertical asymmetry index: F=0.09, p=0.91) or 'stare' OKN (horizontal asymmetry index: F=0.18, p=0.83; vertical asymmetry index: F=0.84, p=0.43). When stimulus size was investigated, there was no overall vertical OKN asymmetry however the vertical stare OKN asymmetry index did appear to be sensitive to target size such that there was a change in the direction of the asymmetry preference from downwards to upwards with an increase in the stimulus size. (vertical 'stare' OKN asymmetry index: F=10.8, p=0.002; vertical 'look' OKN asymmetry index: F=0.58, p=0.49; horizontal

'look' OKN asymmetry index: F=0.03, p=0.85; and horizontal 'stare' OKN asymmetry index F=0.10, p=0.75). This reflected the pattern observed for vertical 'stare' OKN gain in which an upward preference was evident for the larger stimulus size and a downward preference for the smaller stimulus size. Overall however there was no evidence of a significant 0'stare' OKN asymmetry with either target size.

As described previously (section 3.1, 'horizontal and vertical look and stare optokinetic nystagmus symmetry in healthy adult volunteers') an individual subjects' OKN asymmetry was relatively consistent throughout all of the tests, irrespective of target distance or stimulus size, with each individual tending to show a similar degree of upward preference (positive asymmetry index) or downward preference (negative asymmetry index) for all stimuli. This was most obvious for vertical 'stare' OKN asymmetry index. 'Look' OKN asymmetry indices were more tightly distributed (more symmetrical) than 'stare' OKN asymmetry indices. For vertical 'look' OKN, the distribution of asymmetry indices was narrower for the larger stimulus size.

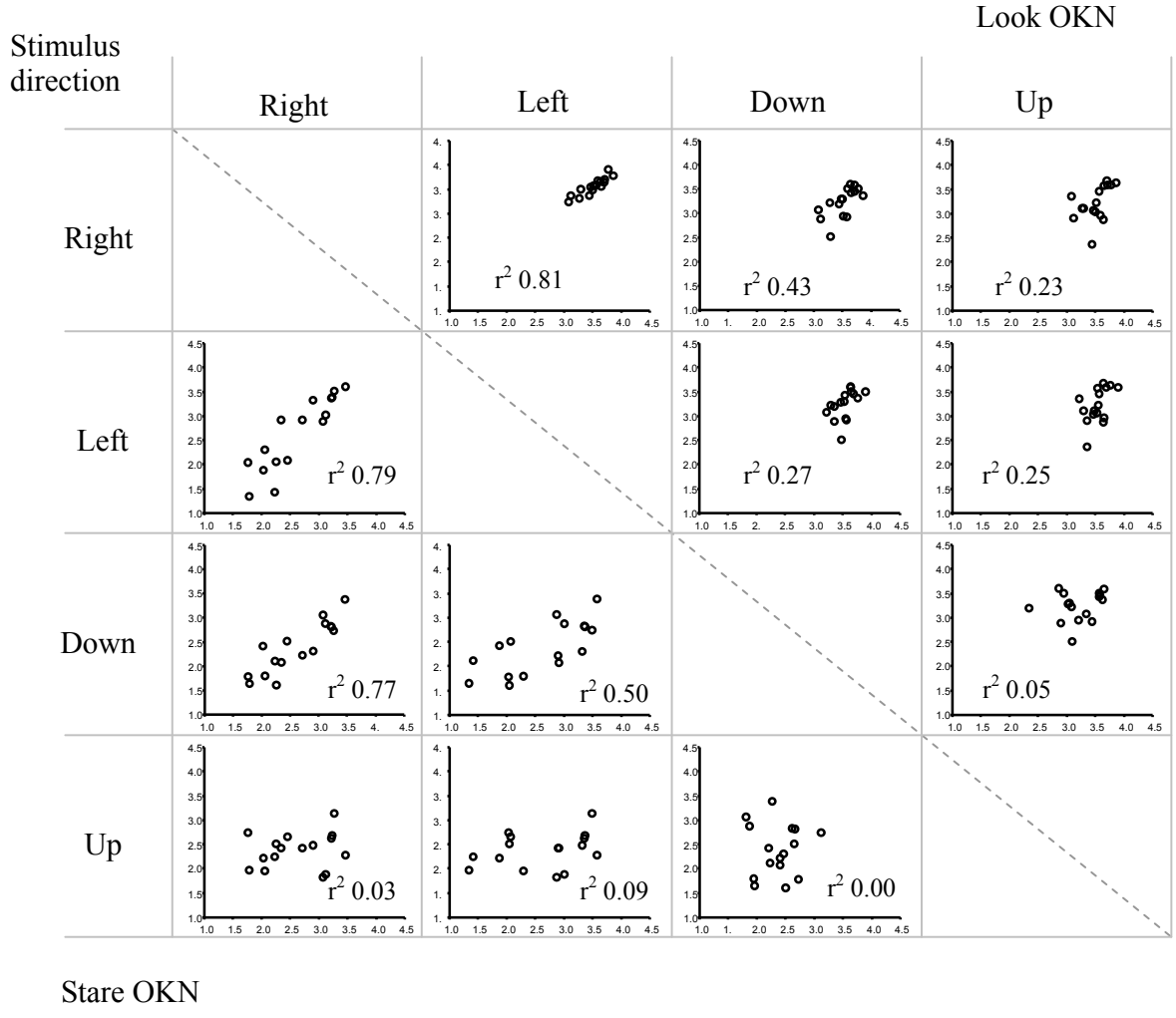
The addition of near vision corrective lenses for the near (0.33m) tests had no significant effect on 'look' OKN gain (rightward: F=0.03, p=0.87; leftward: F=0.82, p=0.37; upward: F=0.98, p=0.32; downward: F=1.46, p=0.23), or 'stare' OKN gain (rightward: F=0.11, p=0.74; leftward: F=3.6, p=0.07; upward: F=0.63, p=0.43; downward: F=0.73, p=0.40). The 'look' asymmetry indices (horizontal asymmetry index: F=0.99, p=0.33; vertical asymmetry index: F=0.02, p=0.89) and 'stare' asymmetry indices (horizontal asymmetry index: F=1.17, p=0.29; vertical asymmetry index: F=0.001, p=0.97) were also unaffected by the addition of a near correction.

Mean log OKN gains were averaged across all trials (without glasses) for stimuli moving in each direction in each individual, with the r^2 values shown below. The results are displayed in figure 3.10. When mean 'stare' OKN gains were investigated a clear difference was observed between the strength of the correlation between the downward and horizontally moving stimuli and the correlation between the stimuli traveling in the upward and horizontal directions. Downward gains were strongly correlated in both the rightward (r^2=0.77) and leftward (r^2=0.50) directions. This was similar to the expected correlation between the rightward and leftward gain (r^2=0.79). In contrast there was little correlation between the upward gain and those gains in the rightward (r^2=0.03) and

leftward directions (r^2=0.09). Surprisingly, there was little correlation between the upward and downward gains (r^2=0.00). In the case of 'look' OKN, this pattern was less clear. As with 'stare' OKN, there was a strong correlation in the horizontal direction (rightward versus leftward, r^2=0.81), and little correlation in the vertical direction (upward versus downwards, r^2=0.05). However when the horizontal and vertical directions were compared the correlation between them was weak, with no correlation of horizontal 'look' OKN with vertical 'look' OKN (down versus right: r^2=0.43, down versus left: r^2=0.27, up versus right: r^2=0.23, up versus left: r^2=0.25).

***Figure 3.10**: The correlations between mean log OKN gains averaged across all trials for each individual, comparing different directions of stimulus movement. For stare OKN there is a clear difference between the correlation between downward OKN and upward OKN in relation to the horizontal directions.*

Scatter plots of mean log gain



3.3.4 Discussion- Investigation 3

We found that stimulus size had a greater effect on OKN responses than distance. All look and stare gains were significantly reduced when viewing the smaller stimulus size, with the vertical gains being affected the most, especially in the upwards direction. This resulted in vertical OKN asymmetry changing significantly with stimulus size, but not with distance. The asymmetry of vertical OKN responses, where present, was relatively consistent for each individual volunteer, with inter-subject differences accounting for much of the variability in vertical asymmetry in 'stare' OKN. When the four directions of gaze were analysed, there was a striking difference in mean 'stare' OKN gain in the upward and downward directions. Downward 'stare' OKN responses were strongly correlated with the horizontal (left and right) responses. In contrast, upward OKN responses were not correlated with the horizontal responses or in the downward direction. This distinction was not observed for 'look' OKN.

Distance appeared to have no significant effect on horizontal 'look' and 'stare' OKN gain, however downward 'stare' OKN gain did seem to be affected by target distance. Vertical 'look' OKN and 'stare' OKN in the upward direction was not dependant on distance. These findings suggest that vergence does not play a role in either 'look' or 'stare' OKN since one would expect horizontal OKN responses to increase as the viewing distance reduced and the angle of convergence increased.

The observation that distance has no effect on horizontal and vertical OKN is at variance with findings reported by **Jagla et al** [147] who found a small but significant difference in horizontal OKN gain in 20 subjects viewing stimuli binocularly at 0.5m compared to 1.5m ($p<0.001$) and 0.5m compared to 2.0m ($p<0.01$) for OKN stimuli only moving in a rightward direction. This discrepancy may be explained by the different experimental set-ups used by Jagla and ourselves. Jagla placed the stimulus projector above the head of the volunteer and moved it nearer the projection screen when testing shorter distances. Consequently, target luminance was not matched for the different distances tested. In our study monocular eye movements were examined in four directions of gaze; right, left, up and down and a rear projection system was used to produce the target stimuli, allowing the target luminance to be matched when the projector was placed at different distances from the screen. In addition, Jagla used a

square wave modulated contrast grating stimulus (width ratio1:2, cycle size 5°) moving at 21°/s, covering a visual field of 1.35x1.4m. We used a sinusoidally modulated contrast grating (cycle size 4.4°, image sizes 80° x 60° and 20° x 15°) moving at a linear velocity of 38.4°/s.

The effects of stimulus size on OKN were greatest for vertical OKN, in particular, upward directed stimuli, leading to a change in vertical asymmetry with the larger target. Our findings are similar to those of **Murasugi et al** [39] who investigated the effects of central and peripheral field stimulation on vertical OKN asymmetry. They found an upward OKN preference with a large target stimulus (61° x 64°), whilst central stimulation with a small OKN target (10° x 6°) resulted in OKN with no asymmetry at all.

Our findings also indicate that the sensitivity of vertical asymmetry to the relative amounts of central and peripheral stimulation also apply to 'look' OKN as well as 'stare' OKN.

In this study we observed that downward stare OKN responses were strongly correlated with horizontal responses (figure 3.11). Whereas upward and downward stare OKN responses are not correlated at all. This may indicate that, functionally, the downward OKN system is more closely related to the horizontal system than the upward system.

The sensitivity of downward and horizontal OKN gain to distance may be related radial optic flow patterns associated with forward locomotion. During forward movement, due to the close proximity of the ground and ground based objects, there are a greater number of 'targets' in the lower visual field compared to the upper visual field (the sky). This is supported by studies in which OKN responses in the lower visual field are compared with the upper field. Superior OKN responses are seen by stimulating the inferior visual field [150]. **Yang et al** demonstrated that grating patterns moving in the ground plane (using a computer monitor lying flat) generate a powerful horizontal vergence and vertical downward version OKN response in humans even under monocular conditions [151]. This may be a powerful pre-programmed OKN response to stabilize gaze whilst moving forwards and account for the sensitivity of the OKN system to downward

moving target stimuli. The effect may be accentuated further if the head is tilted down or during the fixation of ground based objects below the horizon [152].

3.4 Investigation 4: Vertical Stare Optokinetic Nystagmus in Parkinson's Disease

3.4.1 Introduction- Investigation 4

Parkinson's disease is a neurodegenerative disorder characterised by loss of dopaminergic neurons in the basal ganglia with a subsequent reduction in dopamine synthesis.

To our knowledge only three studies in the literature have investigated the effects of Parkinson's disease on OKN. Of these only one investigated vertical OKN (see section 1.3.5 'the effects of Parkinson's disease on OKN').

We investigated horizontal OKN and vertical OKN responses in a group of Parkinson's disease patients and compared the results with an age-matched control group.

3.4.2 Methods- Investigation 4

Fourteen Parkinson's disease patients (11 male, 3 female, age range 35-85 years, mean age 67.8 years) with a Hoehn and Yahr [134] severity scale of 1-3 were recruited for the study from neurology clinics at the Leicester General Hospital, UK (table 3.3). Thirteen of the fourteen were on medication (described in section 1.3.5 'the effects of Parkinson's disease on OKN') at time of investigation whilst none suffered from any known ophthalmic or otological disorder. A control group of fourteen age matched healthy control subjects with no history of neurological, ophthalmic or otological disease (6 male, 8 female age range 43-83, mean 64.9 years) were recruited for comparison.

All OKN target stimuli were projected onto a rear projection screen (1.75m width and 1.17m height) using a VisLab projection system (SensoMotoric Instruments GmbH, Berlin) and Hitachi CP-X958 video projector (1024x768 resolution, 60Hz). Eye movements were recorded using the EyeLink I pupil tracker (described earlier in the 'methods common to all investigations section').

Table 3.3: *Clinical details of the Parkinson's disease patients involved in the study.*

Patients	Age	Sex	Hoehn & Yahr	Disease duration (yrs)	Medication
1	72	Male	1.5	6	L, E
2	63	Male	1	5	L, P
3	71	Female	2	7	L
4	75	Male	2	11	L, P
5	73	Male	1.5	7	L, R
6	68	Male	2.5	7	L, R
7	75	Male	2	<1	L
8	85	Female	2	4	L
9	65	Male	2	6	R, T
10	75	Male	3	7	L, E
11	46	Female	2	7	L
12	69	Male	2	7	L, P, E, A
13	35	Male	1	<1	Untreated
14	78	Male	3	3	L

Medication key: L *levodopa* *E* *Entacapone*
P *Pergolide* *R* *Ropinirole*
T *Trihexyphenidyl* *A* *Amantadine*

Both the Parkinson's disease patients and control subjects viewed the same OKN target stimuli binocularly at 1.2m (resulting in a visual field of ±65° width and ±55° height). Head movements were minimized using a chinrest. OKN eye movement data was recorded for a period of 15 seconds with a gap of at least 15 seconds between each test stimulus to minimize the effects on OKAN (optokinetic after nystagmus) on the subsequent test.

Test stimuli consisted of a square wave modulated contrast grating (spatial frequency = 0.45 cycles/deg) with Michelson contrast of 88% (luminance from 0.88 to 14.3 cd/m^2). The OKN responses were tested in four directions: up, down, leftward and rightwards in random order at linear velocities of 20°/s and 40°/s. All volunteers were encouraged to look towards the centre of the screen whilst keeping the stripes in focus in order to ensure 'stare' OKN was recorded.

Statistical analysis

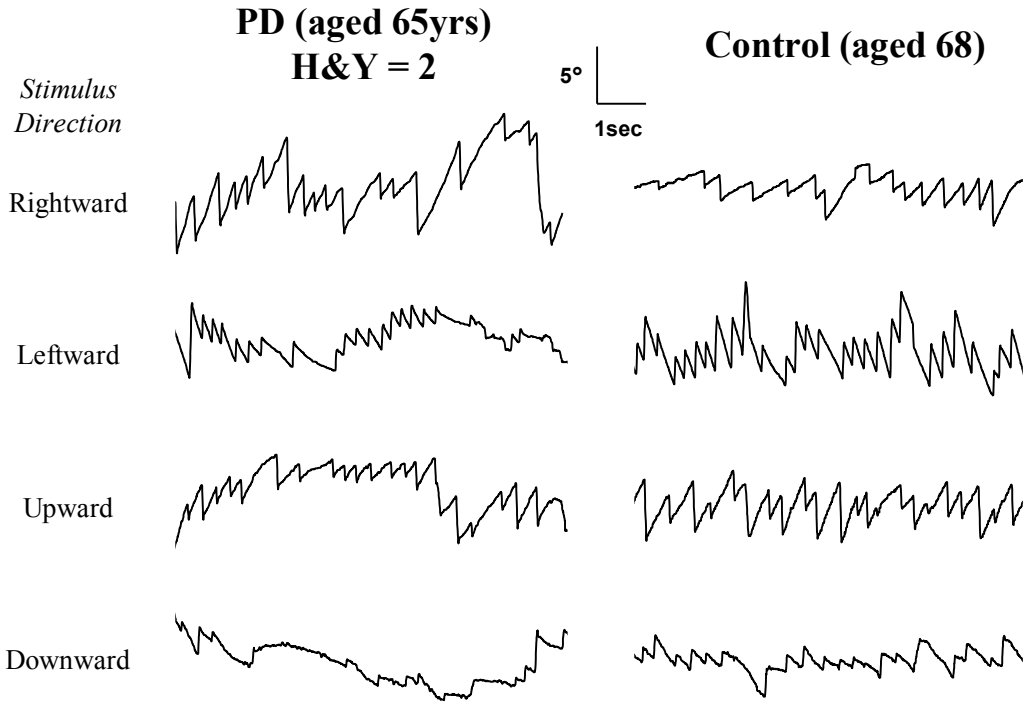
Vertical OKN gains and asymmetries approximated to normal distributions and were tested using linear mixed models including stimulus direction and speed as fixed factors. Post-hoc comparisons were Bonferroni corrected. Horizontal OKN gains and asymmetries (gains and beat frequencies) were not normally distributed in controls and comparisons were made using non-parametric statistics.

3.4.3 Results- Investigation 4

The original eye movement recordings for a 65 year-old Parkinson's disease patient (Hoehn & Yahr = 2) and a control volunteer of 68 years are shown in figure 3.11. Brisk OKN responses consisting of fast and slow phases can be observed in all stimulus directions for the control subject and in rightward, leftward and upward directions for the Parkinson's disease patient. A weak OKN response to downward moving stimuli was observed in the Parkinson's disease patient with less consistent fast and slow phases.

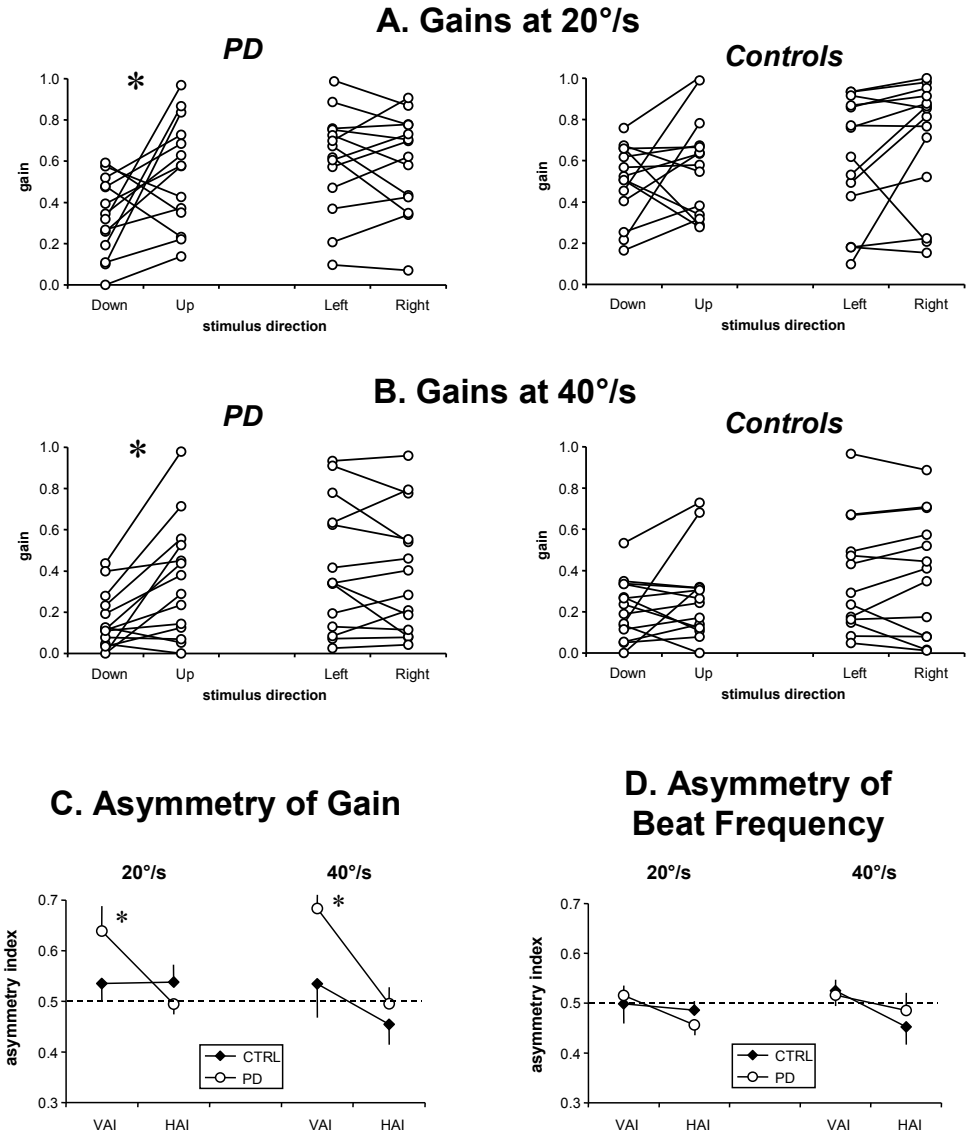
OKN gains for each volunteer are presented in figure 3.12 with the connecting lines indicating the degree of horizontal and vertical asymmetry for target velocities of (A) 20°/s and (B) 40°/s. The OKN responses are clearly reduced for the downward direction compared to the upward, leftward and rightward directions in subjects suffering from Parkinson's disease. The overall effect of this is that there is a vertical asymmetry in Parkinson's disease patients with preference for stimuli moving in the upward direction (F=6.46, p=0.025 for 20°/s and F=12.9, p=0.003 for 40°/s), whereas horizontal OKN gains, although variable between patients, are more symmetrical (F=0.075, p=0.79 for 20°/s and F=0.49, p=0.50 for 40°/s). There was no significant vertical OKN asymmetry (F=1.33, p=0.27 for 20°/s and F=2.33, p=0.15 for 40°/s) or horizontal OKN asymmetry (F=1.23, p=0.29 for 20°/s and F=0.02, p=0.89 for 40°/s) in the age-matched control group of subjects

Figure 3.11: *Original eye movement recordings from a 65-year old PD patient and 68 year old control. Movements upwards on the trace indicate either rightward or upwards eye movements.*



Horizontal and vertical OKN gain (figure 3.12C) and beat frequency (figure 3.12D) asymmetry indices were compared. There was a significantly greater vertical OKN gain asymmetry in Parkinson's disease when compared with the control group of subjects (F=4.45, p=0.044 for 20°/s and F=5.42, p=0.028 for 40°/s) however, when horizontal OKN asymmetry indices were compared, there was no significant difference (F=1.13, p=0.30 for 20°/s and F=0.56, p=0.46 for 40°/s). Beat frequencies were relatively symmetrical in Parkinson's disease and control subjects along the horizontal and vertical axes with no significant difference between the two groups (F=2.87, p=0.10 for 20°/s and F=0.94, p=0.34 for 40°/s along the horizontal axis; and F=0.21, p=0.65 for 20°/s and F=0.030, p=0.86 for 40°/s along the vertical axis). The beat frequencies were similar for each of the stimulus directions at 20°/s and 40°/s (p>0.05 for all) in both the Parkinson's disease group and control group.

Figure 3.12: *Mean OKN gains are shown for individual PD patients and controls in response to stimuli moving at (A) 20°/s and (B) 40°/s. Connecting lines indicate the degree of horizontal and vertical asymmetry for each individual. Parkinson's disease patients showed strong vertical OKN asymmetry especially at 40°/s. The asterisk indicates a significant asymmetry. Mean vertical and horizontal asymmetry indices for Parkinson's disease patients and controls are shown for (C) OKN gain and (D) OKN beat frequency of the fast phases. The asterisk indicates a significant difference between PD patients and controls. Error bars = SEM, HAI = horizontal asymmetry indices and VAI = vertical asymmetry indices.*



3.4.4 Discussion

The main finding is that Parkinson's disease is associated with an upward vertical OKN asymmetry resulting from reduced OKN gains in a downward direction (figure 3.11). The horizontal and upward gains appear to be unaffected (figure 3.12).

Our findings contradict those of **Garbutt et al** [143] who found that the OKN responses of five subjects suffering from Parkinson's disease had OKN responses which were similar to those of control subjects. They found no evidence of a vertical OKN asymmetry in Parkinson's disease.

It is not clear why subjects with Parkinson's disease have a vertical OKN asymmetry, however Parkinson's disease has effects on several other structures in the central nervous system including the occipital cortex and cerebellum. There is evidence that the cerebellum has some dopaminergic innervation [138] [125]. Degeneration of these dopaminergic neurons may result in vertical OKN asymmetry in Parkinson's disease subjects. Further evidence for this come from lesion studies on the cerebellum. Injuries to the flocculus tend to affect early component of OKN (OKNe) and result in vertical nystagmus [3]. It is possible that it is the deficiency in the early component of OKN (OKNe) that produces the vertical OKN asymmetry seen in Parkinson's disease, since OKN consists of a combination of OKNe and a delayed component of OKN (OKNd) (discussed in section 1.3.1 'the neurological control of OKN'). In normal adult subjects OKN responses are dominated by OKNe to such an extent that the only time OKNd becomes evident is in the dark as optokinetic after nystagmus (OKAN) [2]. OKAN is highly asymmetric with reduced downward responses [47] [48]. Therefore if the effects of OKNe are reduced by injury or disease, OKNd will have a greater effect on the overall OKN response, resulting in OKN with a reduced downward OKN response and an upward vertical OKN asymmetry.

It is also possible that degeneration of dopaminergic neurones in the basal ganglia may affect a hitherto unknown pathway involved in the generation of OKN, since the basal ganglia are involved in a number of large cortico-basal ganglia-thalamo-cortical loops. One of which the oculomotor loop is involved in the generation of saccadic eye movements [7].

There was no horizontal or vertical OKN asymmetry seen in our control subjects.

It is possible that some of our 'stare' OKN data is contaminated with 'look' OKN since some of the 'stare' OKN gains approach a value of 1. This would suggest that the mean slow phase velocity of the OKN response is almost identical to the target velocity. From investigation 1 (section 3.1 'horizontal and vertical look and stare optokinetic nystagmus symmetry in healthy adult volunteers') we would expect 'stare' OKN gains to be significantly less than 1. Those OKN responses with unexpectedly high gains are therefore potentially contaminated with 'look' OKN responses, however the OKN data was filtered in a manner identical to that of all of the previous investigations to remove as much erroneous 'look' OKN data as possible. When the raw OKN traces were examined by eye, all of the slow phase responses were consistent with no evidence of any contamination with other forms of OKN response. Despite the surprisingly high gains observed in some subjects, we are confident the data investigated only represents 'stare' OKN.

4. General Discussion and Summary

We performed a comprehensive and thorough investigation into vertical OKN and its asymmetry. An attempt has been made to clarify whether a vertical OKN asymmetry exists, the direction of any asymmetry and the main factors influencing OKN asymmetry.

Rather surprisingly one of the main findings of this paper was that there is no evidence of a clear vertical OKN asymmetry for either 'look' or 'stare' OKN in normal healthy individuals under a variety of experimental conditions. This conclusion contrasts with the findings from the majority of the published literature on the subject, in which there is an upward asymmetry in normal healthy adult subjects. These findings do however support the earlier findings by **Hainline et al**, **Collins et al** and **Calhoun et al** [109-111] who found no vertical asymmetry in normal subjects. There are several possible reasons for why our findings differ from the majority of the published literature [38 39 41 47 48 104-107 116 153].

On performing a systematic review of the literature it was clear that the vertical OKN response and its asymmetry in normal subjects was under investigated and that the conclusions drawn in the literature were tenuous to say the least. When the individual papers were examined it was evident that in a number of studies the sample sizes were too small to drawn any significant conclusions [41 108 114]. In many papers it was not clear whether 'look' or 'stare' OKN was being investigated [38 39 104 106 108-111 114-116] and none stated how the resultant data was analysed and data filtered to rule out the type of erroneous response we encountered in our study. Various eye movement techniques were also employed in the literature, mainly due to technical limitations imposed by the technology of the time, for example EOG recording techniques, which are known to be associated with eyelid artifact. Whilst other recording techniques such as the magnetic search coil technique can be uncomfortable because it requires the experimental subject to wear a contact lens with an electrode embedded in it. An uncomfortable subject is not always a reliable subject. In addition to these potential confounding factors a wide range of experimental conditions have been employed using different target sizes, velocities, contrasts and working distances. This makes it difficult to compare the OKN studies published in the literature and hard to draw any conclusions with regards to vertical OKN

asymmetry. However, some of this ambiguity could be addressed by performing a meta-analysis of the amassed vertical OKN literature.

Overall the vertical OKN asymmetry indices for both 'look' and 'stare' OKN responses were consistent in our investigations despite the fact that they are different eye movements. Interestingly 'look' OKN was more vertically symmetrical than 'stare' OKN. This could be explained by the larger gains associated with 'look' OKN, possibly resulting from a link between 'look' OKN and smooth pursuit, since they both have similarities in their underlying neurological control.

OKN is thought to be under the control of four nuclei, the dorsal (DTN), lateral (LTN) and medial (MTN) terminal nuclei in the midbrain (as discussed in section 1.3.1 'neurological control of OKN'), collectively known as the accessory optic system (AOS), and a fourth nuclei located in the pretectum, the nucleus of the optic tract (NOT). They are not directly connected but tend to operate as three functional groups responding to different directions of motion [2]. The DTN responds to horizontal slip motion, whereas the LTN and MTN respond to vertical motion [3] and are implicated in the generation of vertical OKN [67-69]. The nuclei in NOT are binocularly driven and thought to encode for errors in retinal position, velocity and acceleration [3]. The neurological control of smooth pursuit and the ocular following response are poorly understood, however the striate cortex and the human homologue of the middle temporal visual area (MT) and medial superior temporal visual area (MST) are both thought to play a role in its generation [9]. Interestingly the AOS and the NOT [2 3 9] are also involved in the generation and control of smooth pursuit movements.

Unilateral damage to the NOT results in impaired smooth pursuit [3] and a reduced ipsilateral slow phase OKN velocity, whereas bilateral damage results in reduced horizontal OKN gains in both the nasal and temporal directions [46]. Vertical OKN seems to be unaffected by damage to the NOT [154 155].

When the effects of different target parameters on OKN responses were investigated we found that target distance had no significant effect on the gain or asymmetry of horizontal 'look' and 'stare' OKN. Vertical 'look' OKN and 'stare' OKN gain in an upward direction was also unaffected. However downward 'stare' OKN responses decreased significantly with increasing target distance. This effect was not

great enough to create an up ward vertical OKN asymmetry. Downward 'look' OKN responses were unaffected by target distance.

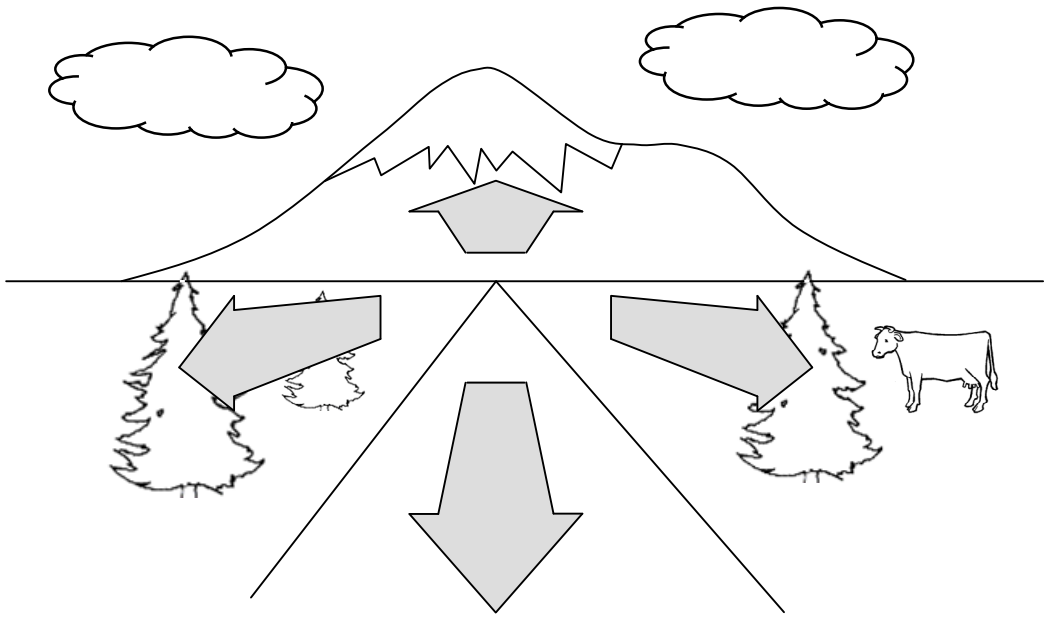
Stimulus size had a much greater effect on horizontal and vertical OKN responses when compared with distance. All 'look' and 'stare' gains were significantly reduced when viewing the smaller stimulus size. Vertical OKN gains appeared to be the most sensitive to target size. An upward preference was seen with larger stimuli whilst a downward preference was noted with the smaller stimulus size. The result was that the vertical OKN asymmetry preference significantly changed with the stimulus size, however overall there was no significant vertical OKN asymmetry. This may well explain why a number of studies in the literature find an upward OKN asymmetry since they tend to used full field or near full field stimulation [41 104-107 153].

When investigating the effects of distance on horizontal and vertical OKN it was evident that downward 'stare' OKN responses were strongly correlated with the left and right horizontal OKN responses. Interestingly upward OKN responses were not correlated with either horizontal or downward OKN responses. This distinction was not observed for 'look' OKN. A possible explanation for the association between downward and horizontal 'stare' OKN responses involves the concept of radial optic flow, whereby motion is space generates movement of the visual field. The nearer the individual is to the stimulus the greater the sensation of movement. Under normal physiological conditions the ground and objects in the lateral visual fields are much closer to the subject than the open sky above. During forward motion objects in the inferior visual field move in a downwards direction, whereas objects in the horizontal plane will produce movements of similar magnitude in right and left visual fields. A consequence of motion induced by objects in close proximity to the observer is that relatively small increases in forward motion are associated with relatively large increases in the sensation of motion. It is possible that 'stare' OKN is a more pure form of OKN allowing us to see this relationship, whereas with 'look' OKN, which is possibly a combination of 'stare' OKN and other eye movements such as smooth pursuit, the association is masked.

The optic flow theory (figure 4.1) would suggest that motion of targets in the lower visual field would be associated with superior OKN responses compared with stimulation of the central field, a finding reported by **Murasugi et al** [150]. More recently

Yang et al [151] demonstrated that grating patterns moving in the ground plane (using a computer monitor lying flat) generate powerful horizontal vergence and vertical downward version OKN response in humans even under monocular conditions, suggesting that 'pre-programmed' OKN responses can be generated based on the optic flow patterns in the ground plane. Although radial optic flow patterns were not investigated in this study, it is possible that the sensitivity of downward OKN responses to distance is related to the specialization of the visual system to downward radial optic flow during forward motion.

Figure 4.1: *A pictorial representation of the functional link between downward and horizontal motion due to closer proximity of the lower visual field. Forward locomotion leads to radial optic flow patterns in which downward motion tends to be closer in velocity to horizontal motion in comparison to upward motion (represented by the length of the arrows).*



The correlation of downward OKN responses with horizontal OKN would suggest that they both have a similar underlying control mechanism. The AOS and NOT seem to be the most likely systems, since horizontal OKN is thought to be under the control of

these nuclei, whilst the LTN and MTN are implicated in the generation of vertical OKN [67-69]. Our findings would seem to support this association particularly for downward motion. The association for upward motion is less clear.

It is also possible that methodological differences could account for the differences we found between our results and those in the published literature. During our series of investigations we used an EyeLink I (SensoMotoric Instruments, GmbH, Berlin, Germany) non-invasive high-resolution infrared video pupil tracker to record eye movement data. Due to technological limitations, earlier studies tended to use electro-oculogram (EOG) recording techniques to record data. This system relies on the fact that the eye has a resting potential, which alters as the eyes move relative to two electrodes place on the eyelids. Therefore when using EOG techniques to measure eye movements, the experimenter is reliant on the eyelids accurately following any eye movement induced by the OKN target stimulus. Spontaneous eyelid movements and blinks will therefore introduce an artifact that can be misinterpreted as an OKN response. Other investigators have used magnetic search coil techniques to record eye movements. This involves an experimental subject wearing either a tightly fitting contact lens, or rubber ring with a coil embedded in it. This method is highly accurate since it is able to directly any measure eye movements. The technique is however quite invasive and potentially uncomfortable especially for subjects not used to wearing contact lenses. Uncomfortable subjects tend to be distracted during investigation, which may well affect the quality of the OKN data recorded.

Subject sample size is also an issue, since many of the published studies use small subject groups (see table 1 in section 1.3.3 ‘vertical OKN’). This is relevant since we found that individuals within the study groups tended to show an idiosyncratic OKN asymmetry response despite the fact that there was no overall vertical asymmetry in the group as a whole. These idiosyncratic asymmetries occurred with both ‘look’ and ‘stare’ OKN under all experimental conditions investigated in this study and were of similar magnitude and direction in each eye, irrespective of which eye was being examined. Therefore it is possible that in those studies where there are only a small number of experimental subjects, any asymmetry result reported could simply be an artifact and not statistically significant. With a larger sample size any reported asymmetry may disappear

The way the OKN data is analysed once it is recorded is crucial when investigating OKN and OKN asymmetries. Our data was analysed using the Spike2 program. Each and every OKN trace was examined and analysed by a single investigator. The beginning and end of each slow phase OKN beat of every OKN trace was marked with a cursor using a computer mouse. In this way the mean slow phase velocity of an OKN trace was calculated by the Spike2 program which simply summed up the slow phase velocity of each individual OKN beat and divided it by the total number of recovery saccades. Since every individual OKN beat was analysed, unusual responses resulting from eyelid twitches and blinks could be identified and excluded from the analysis, increasing the reliability of the results.

During data analysis with Spike2 it was clear that both 'look' and 'stare' OKN traces were contaminated by the alternative form of OKN response. This was despite careful instructions to subjects on how they should view OKN stimuli during 'look' and 'stare' tests. This was most noticeable when analyzing 'look' OKN traces, which typically consisted of two distinct waveforms, a long duration slow phase with infrequent quick phases ('look' OKN), and short duration slow phases with frequent quick phases ('stare' OKN). The short duration 'stare' OKN responses typically followed the long duration slow phase movements of 'look' OKN irrespective of the direction of stimulation. It appeared that this response corresponded to the volunteer attempting to find and 'lock on' to the next OKN stimulus stripe. There was less contamination of the 'stare' OKN data. The contamination could be seen graphically when the slow phase velocity distribution for 'look' and 'stare' OKN responses were displayed on histograms. A bimodal curve was produced with the 'look' OKN data, whereas a single unimodal peak was produced with 'stare' OKN (figure 3.2, section 3.1.3). The first peak (maximum at 0.25-0.3 sec) of the bimodal 'look' OKN curve corresponded with the single peak of the unimodal 'stare' OKN curve (maximum at 0.25-0.3sec). This confirmed the suspicion that the short duration slow phase beats seen during the 'look' OKN tests were 'stare' OKN responses. All OKN data was therefore filtered before final analysis to remove these erroneous results. 'Look' OKN data was classified as that data having slow phase responses of a duration greater than 0.45 seconds, since this duration represented the trough between the two peaks of 'look' and 'stare' OKN on the bimodal 'look' OKN

curve. When analyzing 'stare' OKN, all data with a slow phase duration greater than 0.45 seconds ('look' OKN) was filtered out.

Despite our extensive investigation of vertical OKN, we found no evidence of a horizontal or vertical asymmetry in normal healthy adults, however when Parkinson's disease was investigated, we found an up ward vertical OKN asymmetry resulting from a reduced response to down ward moving stimuli. No horizontal OKN asymmetry was seen.

Our finding of a vertical OKN asymmetry in Parkinson's disease is unique. Of the three studies investigating OKN in the literature [138 142 143] only one investigated vertical OKN. This study by Garbutt et al [143], found that there was no evidence of a vertical OKN asymmetry in Parkinson's disease patients and that their OKN responses were no different from those of normal health adults. Interestingly the other studies investigating OKN also investigated smooth pursuit eye movements. Both found that OKN and smooth pursuit gains were reduced [138 142]. In our study we found the downward OKN gains were reduced resulting in an upward OKN asymmetry. Parkinson's disease is also known to be associated with other oculomotor deficits including a diminished ability to generate volitional saccades and an inability to suppress visually guided saccades [129 130].

Functionally Parkinson's disease is characterized by loss of dopaminergic neurons in the basal ganglia [129-131] with a reduction in striatal dopamine. The underlying pathology is spread throughout the central nervous system [123] and is seen histologically as a loss of pigmented neurons in the basal ganglia with an accumulation of Lewy bodies (eosinophilic proteinaceous intracytoplasmic inclusions) throughout the brain [124 125]. The basal ganglia are involved in five large cortico-basal ganglia-thalamo-cortical loops, two of which are concerned with eye movements, the oculomotor loop, which interacts with the frontal eye fields and parietal posterior cortex before projecting to the superior colliculus and is involved in the generation of saccadic eye movements. The second loop, the dorsolateral prefrontal loop is involved with memory tasks and may play a role in the learning of, and replaying of, eye movements such as saccades [7]. The subthalamic nucleus of the basal ganglia is thought to be the area most closely involved with eye movement [126].

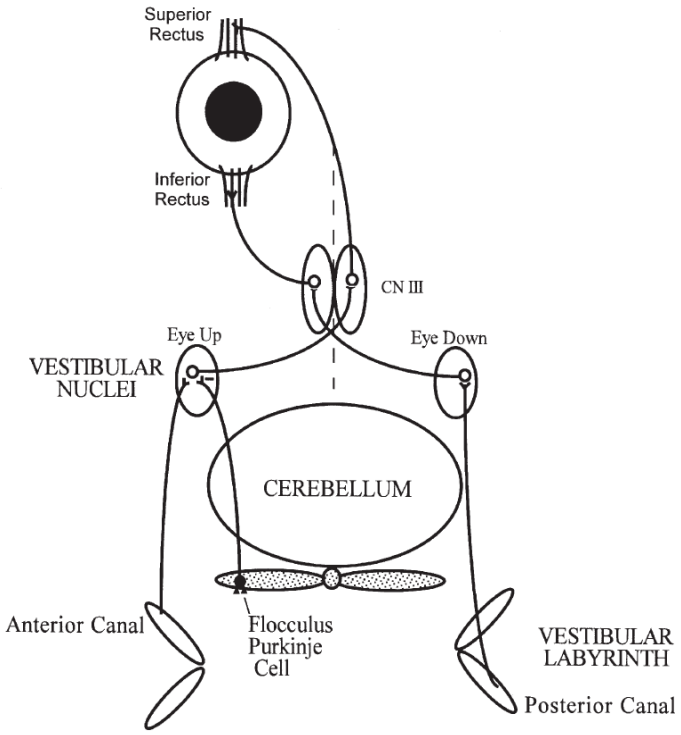


Figure 4.2: *A schematic representation of the pathways responsible for the upward drift of the eyes with corrective downbeat nystagmus. Reproduced from Chapter 10 Leigh & Zee 2007*

It is not clear why only downward OKN was affected in our study, which resulted in a vertical OKN asymmetry in Parkinson's disease. It is possible that the dopaminergic pathways in the basal ganglia play a role in the control of vertical OKN and that with the subsequent degeneration of these cells a vertical OKN asymmetry develops, although why horizontal and up ward OKN responses are unaffected is unclear. It is also possible that Parkinson's disease affects dopaminergic neurons elsewhere in the central nervous system, in particular the cerebellum, since there is evidence from functional magnetic resonance imaging (fMRI) studies that the it is active during OKN stimulation [74]. Lesion studies on the cerebellum also indicate that it is involved in the generation of OKN. Lesions affecting the flocculus tend to affect the early component of OKN (OKNe) [2] and are implicated in the generation of vertical nystagmus [3]. Interestingly the flocculus has a preference for downward movement (figure 4.2) and injuries here tends to evoke upward eye movements initiating a corrective movement in the form of down beat nystagmus [3]. Damage to the nodulus and uvula of the cerebellum tend to affect the delayed component of OKN (OKNd) [2]. Doperminergic neurons have been found in the cerebellum [138]. If these doperminergic neurons are located in the flocculus and are affected by Parkinson's

disease, this would account for the upward asymmetry (downward deficit) seen in our study.

As expected, when horizontal OKN was investigated, we found no evidence of any OKN asymmetry with either look or stare OKN under any test conditions. This is in keeping with the majority of the published literature. It is interesting to note however that a number of individuals in our investigations displayed an idiosyncratic OKN asymmetry with either a temporal ward or nasal ward preference, which was consistent in each eye under a wide range of stimulus parameters. This is a unique finding to our study, however the underlying cause is unknown.

Overall the most striking finding linking all of the investigations in to vertical OKN is the downward OKN response. When we correlated horizontal 'stare' OKN responses with vertical 'stare' OKN, we found that the downward OKN responses were correlated with the left and right responses. Downward 'stare' OKN responses were also the most sensitive responses to a change in target distance. In Parkinson's disease we found that subjects had reduced downward OKN responses. It is not clear why the downward direction is so sensitive, however it could be that vertical OKN, in particular, in the downward direction, is under strong cerebellar control, possibly as a result of radial optic flow.

During our research into OKN we investigated OKN asymmetry under a wide range of experimental conditions with a large sample size, using the EyeLink 1 infra-red pupil tracker to collect the data. This method was chosen as we felt it was the least invasive and most comfortable of all the OKN recording techniques available, and consequently associated with the least number of recording error when compared with other techniques. We ensured the data was rigorously analysed using the Spike2 program, with one investigator assessing each individual OKN trace in each and every experiment to ensure maximum accuracy of the results and to eliminate inter-observer error. We feel our results are robust and that we can comment on OKN and OKN asymmetry with some confidence.

5. References

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