# LOW- AND HIGH-LEVEL MOTION DEFICITS IN AMBLYOPIA:

# STUDIES OF MAXIMUM MOTION DISPLACEMENT

by

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## ABSTRACT

The human visual system comprises two neural pathways, the magnocellular/M and parvocellular/P pathways that process aspects of motion and form perception, respectively. Amblyopia is a developmental condition which may affect an otherwise healthy eye if it experiences abnormal visual stimulation due to ocular misalignment (strabismus), unequal refractive errors (anisometropia), or both. Amblyopia has been associated with deficits in both form and motion perception.

Random-dot kinematograms (RDKs) which are created by shifting a computer-generated dot display in one direction by a given displacement can be used to assess motion processing. Maximum motion displacement (Dmax) is the largest dot displacement at which the direction of motion for a RDK can be correctly discriminated. Strabismic and anisometropic amblyopia represent two distinct subtypes of amblyopia and have been proposed to have different neural substrates. They have also been reported to have different Dmax deficits (Ho et al., 2005).

The intentions of this thesis were: 1) to characterize deficits in Dmax for direction discrimination in the fellow and amblyopic eyes of participants with anisometropic and strabismic amblyopia using psychophysical methods; and 2) to investigate the relationship between psychophysical Dmax deficits and dysfunction in motion-sensitive extrastriate cortex of the M pathway using functional MRI techniques.

The psychophysical results showed that Dmax thresholds are smaller in both amblyopic and fellow eyes for both subtypes of amblyopia relative to controls, although the deficits were greatest for strabismic amblyopia. Functional MRI results revealed decreased extrastriate cortical activation in both the strabismic and anisometropic groups relative to the control group when either eye viewed the RDK stimulus, although the lack of cortical activation was greatest for strabismic amblyopia. Taken together, this evidence suggests that dysfunctional binocular motion processing mechanisms in extrastriate cortex are part of the neural deficit underlying anisometropic and strabismic amblyopia and implies that strabismic amblyopia may be affected to a greater degree.

For both amblyopic groups, there was a robust correlation between depth perception (stereoacuity) and Dmax thresholds. Specifically, direction discrimination was better when stereoacuity was worse. Abnormal binocular integration may have a significant role in predicting motion deficits in both anisometropic and strabismic amblyopia.

**TABLE OF CONTENTS**

## LIST OF TABLES

## LIST OF FIGURES

**Acknowledgements**

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**Co-Authorship Statement**

I was responsible for all aspects of each study in this thesis including the design of experimental methods and procedures, data collection, stastical analysis and interpretation of all results, as well as manuscript preparation.

Deborah Giaschi is listed as a co-author on two papers published in *Vision Research* (Chapters 2 and 3) as well as two manuscripts submitted to *Vision Research* (Chapters 4 and 5). Her role was supervisory only. Her contributions included providing laboratory space and equipment; access to study subjects; obtaining ethics approval and research funding, as well as consultation on experimental methods and results when required.

## CHAPTER 1: INTRODUCTION

Amblyopia is a developmental condition characterized by reduced vision which may affect an otherwise healthy eye during childhood if it experiences abnormal visual stimulation due to visual deprivation, ocular misalignment (strabismus), unequal refractive errors (anisometropia), or both. The abnormal visual experience results in cortical changes within the visual system which are responsible for the visual deficits.

Amblyopia affects 2 to 4% of the population and accounts for more vision loss than ocular diseases and trauma combined in individuals under 45 years of age (Von Noorden & Campos, 2002). Clinically, reduced visual acuity (VA) on standard tests involving letter or shape recognition is the diagnostic indicator of amblyopia. Unilateral amblyopia is characterized by reduced VA in the amblyopic eye with normal VA in the fellow eye when tested through an optimal refractive correction. Amblyopia is typically treated with occlusion therapy. The better-seeing (fellow) eye is patched so that only the affected (amblyopic) eye receives visual stimulation. If this is initiated within the critical period(s) of vision development (Daw, 1998) prior to approximately age 8, vision in the amblyopic eye can improve. However, occlusion therapy is not always effective and is less effective if initiated after the critical period of visual development. If treatment is delayed or ineffective, then the cortical changes that occur in response to early abnormal visual experience persist into adulthood.

The human visual system comprises at least two neural pathways that continue to develop postnatally. Aspects such as motion and form perception are thought to involve the magnocellular (M) pathway and parvocellular (P) pathway, respectively. Therefore, abnormal visual experience early in development could cause deficits in either (or both) motion and form perception. One can assess motion perception using random dot kinematograms (RDKs) which are computer-generated dots that appear to move when a dot display is shifted in one direction by a given displacement in each subsequent frame. Maximum motion displacement (Dmax) is the largest dot displacement in a RDK at which direction of motion can be correctly discriminated. If the dot displacement is too large then the direction of motion becomes quite difficult to discriminate.

Strabismic and anisometropic (unilateral) amblyopia likely represent two distinct subtypes of amblyopia. Anisometropia creates a blurred image in one eye relative to the other whereas strabismic amblyopia results from a misalignment of one eye relative to the other. Due to their differing etiologies, it is not surprising that the two types of amblyopia have been proposed to differ in their underlying neural correlates and have been reported to exhibit different motion deficits (e.g. Ho et al., 2005). On a neural level, the two subtypes of amblyopia differ in the neuronal receptive field properties specific to the amblyopic eye, and the degree to which there is cross-talk between neurons from each eye. In general, anisometropic amblyopia shows a higher loss of neurons with receptive fields tuned to high spatial frequencies (especially in the amblyopic eye), and greater sparing of binocular neurons (which respond to input from either/both eyes) than strabismic amblyopia. However, the entire neural basis of amblyopia is still not understood. There is evidence that, at least for motion tasks, perceptual deficits affect the fellow eye (Ho et al., 2005) despite normal visual acuity which implicates binocular cortical regions. Furthermore, motion tasks involve cortical mechanisms that differ from those studied clinically. Motion deficits could potentially be of clinical relevance in the diagnosis or treatment of amblyopia; but this is not possible until the motion deficits are better characterized and the cortical mechanisms underlying them are better understood.

***The goals of this thesis were to:***

**1) Characterize direction discrimination deficits by measuring Dmax in the fellow and amblyopic eyes of participants with anisometropic and strabismic amblyopia using psychophysical techniques**

**2) Investigate the relationship between psychophysical Dmax deficits and dysfunction of the extrastriate cortex of the M/dorsal stream using functional neuroimaging techniques.**

The results (summarized in Section 1.6) are significant because they imply that the different Dmax deficits reported in anisometropic and strabismic amblyopia are more likely explained by subtype differences in the extent of residual binocular function than

by differences in the nature of the receptive field losses within the M/dorsal processing pathway.

### 1.1 Parallel processing in the human visual system

The magnocellular (M) and parvocellular (P) pathways begin subcortically in the retina (see Figure 1.1) and project to separate yet interacting regions in the primary visual cortex (V1) that process the different attributes of visual stimuli (reviewed in Shapley, 1990). Beyond V1, the M and P pathways continue into extrastriate cortex, respectively, as the dorsal and ventral streams (Ungerleider & Mishkin, 1982). M/dorsal and P/ventral pathways are the parallel neural pathways governing, respectively, temporal (e.g. motion, timing) and spatial (e.g. shape, localization) aspects of visual perception (Merigan & Maunsell, 1993; Ungerleider & Mishkin, 1982; Zeki, 1978). These pathways have different periods of development (Atkinson, 1992) and likely have different critical periods or windows of neural plasticity when they are vulnerable to changes such as those induced by abnormal visual stimulation or by amblyopic treatment (Daw, 1998). Therefore, abnormal visual experience early in development could cause deficits to either of the pathways before the V1 (subcortical), at V1 (striate cortex), or beyond V1 (extrastriate cortex). It is generally accepted that V1, and not the subcortical pathways, is the primary site of dysfunction in amblyopia (reviewed in Hess, 2001).

From V1, the M/dorsal stream projects to the extrastriate motion processing area V5/MT, the site that integrates local motion signals into a global percept (De Yoe & Van Essen, 1988; Newsome & Pare, 1988), then dorsally on to the posterior parietal cortex (PPC). Because directionally selective neurons are not found in the visual system prior to V1 (DeYoe & Van Essen, 1988), motion perception deficits in amblyopia likely represent abnormal function within V1 or in motion-sensitive extrastriate areas. Figure 1.1 provides a general overview of the M/dorsal and P/ventral streams.

# Two visual processing pathways

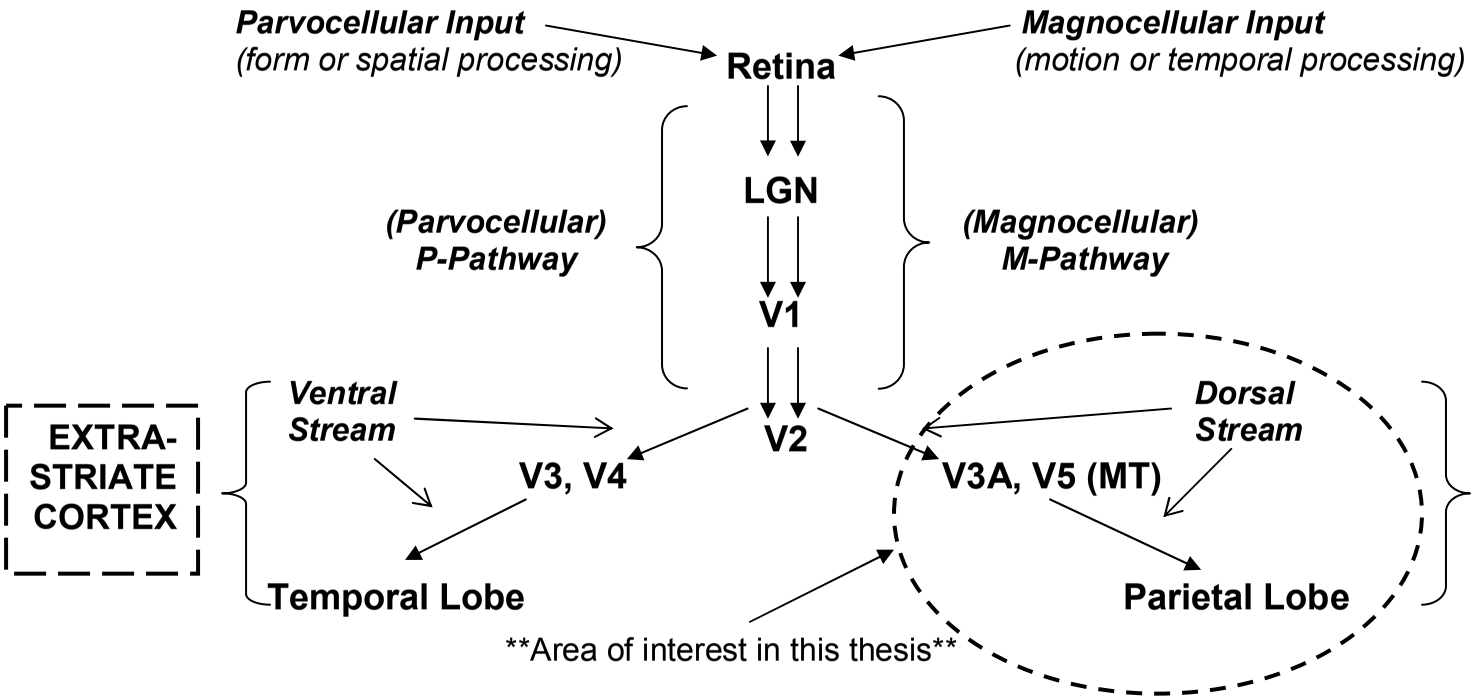


**Figure 1.1:** General overview of M/dorsal and P/ventral streams

## 1.2 Subtype differences in studies of animal neurophysiology

Strabismic and anisometropic (unilateral) amblyopia likely represent two distinct subtypes of amblyopia. Anisometropia creates a blurred image in one eye relative to the other and has been classified as a mild form of deprivational amblyopia[1]. Both eyes receive visual input, but images between the two eyes differ in clarity. Strabismic amblyopia results from a misalignment of one eye relative to the other. In order to eliminate diplopia (double vision) due to the ocular misalignment, central suppression of the deviated eye is common. Therefore, in strabismic amblyopia, both eyes *may* have a clear visual image but the strabismic eye receives less visual input because it is suppressed (visual input from this eye is ignored) whenever the two eyes are used simultaneously (Sireteanu, 2000). As a result of prolonged visual deprivation or suppression, the affected eye is hindered in its development resulting in visual deficits which, without appropriate treatment, remain permanent. Due to their differing etiologies, it is not surprising that the two types of amblyopia have been proposed to differ in their underlying neural correlates.

To understand amblyopia in humans, researchers study neurophysiology in animals with visual systems which mature postnatally, and have similar psychophysical properties to those of humans. Therefore, the visual systems of these animals are also susceptible to cortical changes resulting from abnormal visual experience after birth. V1, the first site of neural dysfunction in amblyopia, comprises monocular neurons which are sensitive to stimulation from one eye only; as well as binocular neurons which respond to stimulation from either or both eyes (Smith, Chino, Ni, Cheng, Crawford & Harwerth, 1997). This brain region is unique in that it is the first site in the visual system where visual input from both eyes is integrated. Studies of neurophysiology in macaque monkeys with surgically induced strabismus or simulated anisometropia have reported visual acuity and contrast sensitivity deficits in individual neurons that respond to stimulation in the amblyopic eye (Kiorpes, Kiper, O'Keefe, Cavanaugh, & Movshon, 1998).[2] For the amblyopic eye, the reduction in contrast sensitivity relative to eyes with

[1] Deprivational amblyopia is a third subtype of amblyopia that may be induced by significant visual obstruction, such as with congenital cataract, but it is not a focus of the research presented here. Therefore, it is occasionally referenced but not discussed in detail throughout this thesis.

[2] Contrast sensitivity represents the lowest contrast level at which a sinusoidal grating (alternating dark and light bars of equal width) may be perceived. It differs for gratings of different spatial frequencies. Low

normal vision generally becomes more pronounced with higher spatial frequencies. The spatial tuning of neurons responsive to the fellow eye may not show the same high spatial frequency losses.

There have been reports of reduced numbers of binocular neurons in V1 for both anisometropic and strabismic amblyopia (Kiorpes et al., 1998; Smith et al., 1997). These neurons are essential for integrating information from each eye. Depth perception (stereopsis) losses are a result of poor binocular integration and this can be disrupted in both types of amblyopia. The extent of loss in monocular neurons, however, may differ in anisometropic and strabismic amblyopia. Anisometropic amblyopia is associated with greater deficits in monocular neurons (especially tuned to high spatial frequencies) corresponding to the amblyopic eye than the fellow eye (Kiorpes et al. 1998; Kiorpes & McKee, 1999). In contrast, monocular neurons responding to the amblyopic and fellow eye are equally deficient in strabismic amblyopia. Despite this equal neural representation, the amblyopic eye in strabismic amblyopia has been shown to exhibit greater perceptual (or behavioural) deficits than the fellow eye - more extensive than predicted from the physiological deficits in V1. Because the behavioural deficits can not be fully explained by corresponding physiological deficits of monocular neurons in V1, involvement of brain regions beyond V1 (extrastriate cortex) has been proposed to explain the additional losses observed in strabismic amblyopia (Kiorpes et al., 1998; reviewed in Kiorpes & McKee, 1999). This is a viable theory since extrastriate cortex has a larger number of binocular neurons than V1 and suppression mechanisms, in strabismic amblyopia especially, affect binocular integration.

Studies in cats with induced visual deprivation or strabismus are consistent with findings in macaque, and also show differences in the underlying neurophysiology of anisometropic and strabismic amblyopia. There are fewer single neurons responsive to the amblyopic eye in cats and the extent of monocular cell loss in striate cortex is much greater with visual deprivation than with surgically induced strabismus (Chino, Shansky,

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spatial frequencies represent gratings comprised of thick bars and high spatial frequencies represent gratings comprised of narrow bars. Visual acuity is the grating with the smallest bar width that is still discernible when presented at 100% contrast.

Jankowski & Banser, 1983). Neural deficits have also been reported in extrastriate areas of cat cortex (Schröder, Fries, Roelfsema, Singer, & Engel, 2002).

Decreased activity in extrastriate cortex may be a downstream effect from V1 due to fewer functional neurons; abnormal neural firing rates from neurons receiving input from the amblyopic eye; and/or loss of or atypical organization of neural connections. In extrastriate cortex, primary deficits could be fewer or less responsive neurons and/or abnormal neural connections relative to those with normal vision (for discussions see Kiorpes and McKee 1999; Levi 1991). One other proposed explanation for reduced neural activity in extrastriate cortex from studies of cat neurophysiology is lack of synchronization in neuronal responses within V1 (Roelfsema, König, Engel, Sireteanu & Singer, 1994).

### 1.3 Psychophysical deficits in amblyopia

In addition to visual acuity and contrast sensitivity losses that are observed in both anisometropic and strabismic amblyopia, other perceptual deficits have been associated with amblyopia from psychophysical investigations, many of which implicate extrastriate areas of the P/ventral and M/dorsal streams. (The references cited below represent only a few examples from the extensive volume of literature that has reported psychophysical deficits in amblyopia.)

Much research has focused on characterizing form perception deficits and the cortical mechanisms underlying these deficits in amblyopic eyes. The deficits include losses in contrast sensitivity and VA, difficulties with orientation discrimination (reviewed in Levi, 1991) as well as spatial distortion (Barrett, Pacey, Bradley, Thibos & Morrill, 2003). McKee, Levi, and Movshon (2003) found that amblyopic individuals with no residual binocular function had better monocular contrast sensitivity and reduced optotype[3] and vernier acuity[4] relative to amblyopic individuals with residual binocular function when subjects were matched for a given level of grating acuity. They suggest that contrast sensitivity is a measure of low level visual processing in V1 and that optotype and

[3] Optotype visual acuity is a measure of visual acuity based on shape recognition such as letters on a vision chart (the arms on a letter “E”, for example, need to be the same as the width of a dark bar in a sinusoidal grating in order for optotype and grating visual acuity to be comparable measures).

[4] Vernier acuity is the ability to discriminate a discontinuity in a line or the misalignment of a segment of a line. Vernier acuity is generally a more sensitive measure than optotype or grating acuity and is not usually comparable to the latter measures.

vernier acuity reflect higher processing occurring in extra-striate cortex. These deficits appear to support extra-striate involvement in the P/ventral pathway.

Different psychophysical deficits may be associated with anisometropic and strabismic amblyopia which reflects the differences in underlying etiology. Most of the deficits associated with strabismus are attributed to ocular misalignment and reduced binocular integration. Although they are less common in anisometropic amblyopia, strabismic amblyopia is often associated with deficits such as anomalous retinal correspondence, eccentric fixation and unsteady fixation, in addition to suppression under binocular viewing conditions (summarized in Asper, Crewther & Crewther, 2000). Spatial vision losses especially pertaining to strabismic amblyopia include vernier acuity (spatial localization) (McKee et al., 2003), positional uncertainty (uncorrelated cortical maps from each eye) (Hess, McIlhagga & Field, 1997), global form perception (Hess, Wang, Demanins, Wilkinson & Wilson, 1999; Simmers, Ledgeway & Hess, 2005), and spatial distortions (Barrett et al., 2003). Crowding or contour interaction is evident in both types of amblyopia but has been reported to be more severe for strabismic amblyopia (Hess et al., 1997) than anisometropic amblyopia (Hess & Demanins, 1998).

Although rarely tested clinically, there is growing evidence that motion perception is also impaired in amblyopia. Reports of abnormal motion processing include deficits involving hyperacuity thresholds for oscillatory movement (Buckingham, Watkins, Bansal & Bamford, 1991; Kelly & Buckingham, 1998); global motion (Ellemberg, Lewis, Maurer, Brar & Brent, 2002; Simmers, Ledgeway, Hess & McGraw, 2003; Simmers et al., 2005); motion-defined form (Giaschi, Regan, Kraft & Hong, 1992; Ho, Giaschi, Boden, Dougherty, Cline & Lyons, 2005); motion after-effect (Hess, Demanins & Bex, 1997); maximum motion displacement (Ho & Giaschi, 2006; 2007); and attentive motion tracking (Ho, Paul, Asirvatham, Cavanagh, Cline & Giaschi, 2006). These deficits may implicate involvement of extrastriate regions of the M/dorsal stream in the neural impairment underlying amblyopia.

### 1.4 Neural correlates of amblyopia in humans

Functional magnetic resonance imaging (fMRI) is a non-invasive, neuroimaging technique that is used to indirectly detect changes in neural activity in the human brain.

In most fMRI studies, neuronal activity is detected using the blood oxygenation level dependent (BOLD) contrast method (reviewed in Logothetis, 2002). The basic premise is that active neurons are associated with an increase in regional cerebral blood flow. Because the influx of oxygenated blood is not fully consumed by active neurons, there is a relative decrease in concentration of deoxyhemoglobin within this area. Deoxyhemoglobin is paramagnetic and this change in concentration creates a local increase in the MR signal near active neurons. Given that it is non-invasive, fMRI is a useful tool that has been frequently used to identify brain regions associated with specific psychophysical deficits in amblyopia (e.g. Barnes, Hess, Dumoulin, Achtman & Pike, 2001; Muckli, Kieß, Tonhausen, Singer, Goebel & Sireteanu, 2006; Sireteanu et al., 1998). Brain activity is monitored while the specific stimuli are viewed. A structural MRI scan sequence provides no information about neural activity, but provides much higher spatial resolution images of brain anatomy than is possible with fMRI. Usually functional MRI and structural MRI data are superimposed to more accurately localize the active brain regions.

Human functional neuroimaging studies have shown evidence of abnormal neural activity in V1 in adults with amblyopia. Using positron emission tomography and fMRI techniques, human amblyopia has been shown to be associated with reduced cortical activity in V1 including reduced ocular dominance columns corresponding to the amblyopic eye. Reduced ocular dominance columns indicate a loss in the number of monocular neurons that are responsive to visual stimulation in the amblyopic eye. Other reports include decreased extent of cortical activation corresponding to stimulation in amblyopic eyes (especially for high spatial frequency stimuli in anisometropic amblyopia); reduced binocular (stimulation to both eyes) neural responses (e.g., Algaze, Roberts, Leguire, Schmalbrock & Rogers, 2002; Barnes et al., 2001; Demer, Grafton, Marg, Mazziotta & Nuwer, 1997; Demer, Von Noorden, Volkow & Gould, 1988; Goodyear, Nicolle, Humphrey & Menon, 2000; Lee et al., 2001).

Using an automated computational method in the analysis of structural MRI images called voxel-based morphometry, Mendola and colleagues (2005) have shown structural changes associated with amblyopia. They found reduced gray matter volume in the striate and extrastriate visual cortex of children with strabismic and anisometropic amblyopia. It is uncertain whether these structural differences in amblyopia are a neural

representation of contrast sensitivity or stereoacuity losses (i.e. loss of monocular or binocular neurons) or if they are attributed to both types of losses.

There are a number of fMRI studies showing that cortical abnormalities in amblyopia extend to regions beyond V1. Extrastriate areas involved in form perception (Imamura et al., 1997; Lerner et al., 2003, 2006) and motion perception (Bonhomme et al., 2006) have been shown to exhibit atypical activation patterns which supports psychophysical evidence for deficits in these areas. It is not known the extent to which the high-level extrastriate deficits are associated with the low-level V1 deficits in humans. They may be secondary to impaired input from V1 or they could be primary deficits that affect top-down processing and influence activity in V1. Structural MRI in children with amblyopia has also shown changes in morphology in extrastriate parietal–occipital (M/dorsal stream) and ventral temporal (P/ventral stream) cortex, suggestive of dysfunction in both high-level form and motion perception pathways (Mendola et al., 2005).

### 1.5 Fellow eye deficits & binocularity

As one progresses through the visual pathway beyond area V1 into extrastriate cortex, a higher proportion of neurons are binocular (Zeki, 1978). Animal models have shown that amblyopia occurs in association with reduced numbers of binocular neurons in V1 and it is likely that the number of binocular neurons in extrastriate cortex is also affected. The extent to and manner in which binocular neurons in higher visual processing areas are affected by abnormal experience during development is not yet clear. Thus, understanding perceptual deficits in the fellow eye may be helpful in determining the nature of binocular neuron involvement in extrastriate cortex.

The fellow eye is often assumed to have normal visual function because it demonstrates normal VA. This assumption is not valid as numerous reports have claimed abnormal perception of form (Davis, Sloper, Neveu, Hogg, Morgan & Holder, 2003; Kandel, Grattan & Bedell, 1980; Kovacs, Polat, Pennefather, Chandna & Norcia, 2000; Leguire, Rogers & Bremer, 1990; Lewis, Maurer, Tytla, Bowering & Brent, 1992) and motion (Ellemberg et al., 2002; Giaschi et al., 1992; Ho & Giaschi, 2006, 2007; Ho et al., 2005, 2006; Simmers et al., 2003, 2006).

Fellow eye deficits likely reflect abnormalities associated with binocular mechanisms. Binocular neurons are not dependent on specific input from only one eye but instead can be stimulated through input from either eye. One might speculate that deficits in the fellow eye could result from a) transfer between the amblyopic and fellow eye through remaining binocular neurons (Leguire et al., 1990); and/or b) abnormal or modified development of neurons responding to fellow eye stimulation due to abnormal binocular interactions and/or competition (Crewther & Crewther, 1993; Kiorpes & McKee, 1999 (review), McKee et al., 2003). Furthermore, perceptual deficits in the fellow eye could be induced, at least in part, by visual deprivation of that eye during occlusion therapy. They can not, however, be accounted for by reduced VA because, in true unilateral amblyopia, VA is only reduced in the amblyopic eye.

Giaschi and colleagues (1992) previously reported very robust deficits in the fellow eyes of amblyopic children (aged 4 to 14 years) on a random-dot, motion-defined letter identification task (letters are only visible when the dots outside move in a direction opposite to the dots inside the shape). It was unclear whether these deficits were related to the form perception deficits commonly associated with amblyopia or whether they were related to a deficit in motion perception. To investigate the possibility of general motion processing deficits in the fellow eye, Ho and colleagues (2005) looked at performance in the fellow eyes of amblyopic children on three specific psychophysical tasks chosen to represent different aspects of motion processing: global motion[5], motion-defined form, and Dmax. The findings suggested that deficits in motion processing were prevalent in the fellow eye of children with unilateral amblyopia despite measures of normal visual acuity in that eye. A deficit on at least one of the three motion tasks was evident in the fellow eye of 57% of the 21 amblyopic children tested. The results confirmed robust deficits of motion-defined form in the fellow eye but also revealed that global motion perception deficits were significantly correlated to stereoacuity (those with poorer stereoacuity performed better), and that Dmax deficits appeared related to etiology present (abnormally high Dmax with anisometropia and

[5] Global motion is a motion task that involves RDKs. It is a measure representing the percentage of dots on the screen that must move in a given direction (e.g. upwards) amongst the remaining randomly moving noise dots, for the overall direction of motion to be accurately perceived (i.e. upwards). For Dmax, all dots move in the same direction but as the dot displacement increases, direction of motion "appears" to be less uniform and is harder to discriminate.

abnormally low Dmax with strabismus). It was concluded that extrastriate motion-sensitive brain areas are likely part of the neural substrate underlying both strabismic and anisometropic amblyopia. Differences in the observed deficits may be due to the known neurophysiological differences between anisometropia and strabismus or due to differences in the extent of abnormal binocular integration. In one of the largest studies of amblyopia to date (N=427), McKee and co-authors (2003) found that performance on several psychophysical tasks involving spatial vision (visual optotype acuity and contrast sensitivity) depended more on extent of residual binocularity and/or severity of amblyopia, rather than the subtype of amblyopia.

### 1.6 Thesis overview

Despite immense progress, many aspects of amblyopia are still not well understood. It is not clear the extent to (or manner in) which the extrastriate M/dorsal pathway is affected in amblyopia since most psychophysical deficits reported have been in spatial aspects of vision or form perception. Whether the reported extrastriate deficits are attributed to receptive field abnormalities (e.g. spatial frequency tuning; number of cells) of neuronal populations within the primary visual cortex or to abnormal binocular integration and loss of binocular neurons remains unknown. Furthermore, it is not certain whether the extrastriate deficits represent a primary cortical deficit or whether they are a secondary deficit resulting from impairments in V1.

The Ho et al. (2005) study only looked at motion deficits in the fellow eye. It is important to establish the nature of these deficits in the amblyopic eye also. If dysfunction in the properties of monocular neurons is primarily responsible for the psychophysical deficits then one might expect performance in the amblyopic eye to be more severe than in the fellow eye. However, if the deficits are related to abnormal binocular function, then one might expect psychophysical performance to be similar in amblyopic and fellow eyes. The former would implicate neural deficits in V1 and the latter may implicate neural deficits in extrastriate cortex, which has more binocular neurons than V1.

There have been previous reports of global motion deficits (Simmers et al, 2003; 2005) and motion-defined form deficits in the amblyopic eye (Giaschi et al., 1992) but there are no reported studies investigating Dmax for direction discrimination in amblyopia. It

has been proposed that Dmax is a psychophysical correlate for the spatial extent of the involved motion detectors (i.e. the size of the receptive fields). Motion detectors are tuned to be spatial frequency dependent (Baker & Cynader, 1986). Dmax may be proportional to the lowest spatial frequency present in a RDK which would involve the largest motion detectors (Bischoff & Di Lollo, 1990). In other words, a larger Dmax value would correspond to larger receptive fields which are tuned to lower spatial frequencies. Because Dmax deficits seemed to depend on the subtype of amblyopia present and to involve the so-called "normal" fellow eyes, this task was chosen because of its potential to further our understanding of the different neural substrates underlying deficits of motion perception in anisometropic and strabismic amblyopia; and to provide insight into the possible link between binocular function and motion perception. Differential Dmax deficits between: 1) the two subtypes of amblyopia may be related to the different proposed neurophysiological models for anisometropic and strabismic amblyopia (i.e. greater loss of monocular neurons responding to high spatial frequencies in anisometropic amblyopia than strabismic amblyopia); and 2) the amblyopic and fellow eyes may provide insight into the extent to which poor binocular integration is responsible for the observed deficits. Dmax for direction discrimination is an aspect of motion that most likely involves motion-sensitive regions beyond V1 and offers a means to investigate the nature of M/dorsal extrastriate neural deficits underlying human strabismic and anisometropic amblyopia.

***The overall objectives & hypotheses of the experiments presented in this thesis are summarized below:***

**Objective 1:** To characterize psychophysical Dmax deficits in the amblyopic and fellow eyes of participants with amblyopic and strabismic amblyopia.

**Hypothesis 1:** Deficits will be greater in strabismic amblyopia than anisometropic amblyopia in both fellow and amblyopic eyes. This hypothesis is based on previous findings of Dmax deficits in the fellow eye (Ho et al., 2005) which implicate involvement of binocular extrastriate brain regions, and studies suggesting extrastriate deficits to be greater in strabismic than anisometropic amblyopia.

**Significance:** The approach used to test this hypothesis in Chapters 2 and 3 was to conduct studies measuring and comparing Dmax thresholds in both eyes of children with anisometropic and strabismic amblyopia. The thresholds were compared to those of age-matched control children. The results showed that Dmax deficits existed in both amblyopic and fellow eyes relative to control eyes in anisometropic and strabismic amblyopia suggesting involvement of extrastriate brain regions with binocular input. The strabismic group performed worse relative to the control group than the anisometropic group which supports the hypothesis above.

**Objective 2:** To explore with fMRI techniques whether deficits in extrastriate brain regions of the M/dorsal stream are indeed part of the neural substrate underlying psychophysical Dmax deficits in strabismic and anisometropic amblyopia.

**Hypothesis 2**: Cortical activation patterns in the M/dorsal stream will show greater differences in extrastriate cortex than V1 when comparing neural activity in strabismic and anisometropic amblyopia with controls. Reduced extent of cortical activation in strabismic amblyopia relative to control and anisometropic groups is likely to be observed.

**Significance:** The approach used to test this hypothesis in Chapters 4 and 5 was to conduct studies investigating cortical activation while viewing RDK stimuli displaced at Dmax using fMRI techniques. This was first done in a group of control participants only (Chapter 4) to confirm that the RDK stimuli stimulated the desired extrastriate brain regions in normal observers. The next experiment (Chapter 5) assessed a different group of controls as well as 2 amblyopic groups: anisometropic and strabismic. Both the strabismic and anisometropic groups showed less cortical activation in extrastriate brain regions relative to the control group regardless of which eye was viewing the RDK stimulus. The strabismic group showed decreased activity to a greater extent than the anisometropic group. The findings provide evidence to support the theory that extrastriate deficits exist in the M/dorsal stream in both anisometropic and strabismic amblyopia and that they may affect strabismic amblyopia to a greater degree.

## 1.7 References


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# CHAPTER 2: DEFICIENT MAXIMUM MOTION DISPLACEMENT IN AMBLYOPIA[1]

## 2.1 INTRODUCTION

Amblyopia is a developmental condition that may affect a healthy eye during childhood if it is deprived of normal visual stimulation due to visual deprivation, ocular misalignment (strabismus) and/or unequal refractive errors (anisometropia). Clinically, reduced visual acuity (VA) on standardized tests involving letter or shape recognition is the diagnostic indicator of amblyopia. Unilateral amblyopia is characterized by reduced VA in the amblyopic eye with normal VA in the fellow eye, when tested through an optimal refractive correction.

Motion perception is rarely tested clinically, but emerging research evidence suggests that it is not spared in amblyopic eyes (Buckingham, Watkins, Bansal & Bamford, 1991; Ellemberg, Lewis, Maurer, Brar & Brent, 2002; Giaschi, Regan, Kraft & Hong, 1992; Hess, Demanins & Bex, 1997; Ho, Giaschi, Boden, Dougherty, Cline & Lyons, 2005; Ho, Paul, Asirvatham, Cavanagh, Cline & Giaschi, 2006; Kelly & Buckingham, 1998; Schor & Levi, 1980a, 1980b; Simmers, Ledgeway & Hess, 2005; Simmers, Ledgeway, Hess & McGraw, 2003; Simmers, Ledgeway, Mansouri, Hutchinson & Hess, 2006; Steinman, Levi & McKee, 1988). It has been suggested that motion perception deficits may provide a measure of neural change and visual loss more sensitive than form perception deficits (Kelly & Buckingham, 1998).

The fellow eye in amblyopia is often assumed to have normal visual function because it demonstrates normal VA. This assumption is likely not valid as numerous studies have reported subtle deficits in form perception (Davis, Sloper, Neveu, Hogg, Morgan & Holder, 2003; Kandel, Grattan & Bedell, 1980; Kovacs, Polat, Pennefather, Chandna & Norcia, 2000; Leguire, Rogers & Bremer, 1990; Lewis, Maurer, Tytla, Bowering & Brent, 1992; Wang, Ho & Giaschi, 2006) and more robust deficits in motion perception (Ellemberg et al., 2002; Giaschi et al., 1992; Ho et al., 2005, 2006; Kelly & Buckingham, 1998; Simmers et al., 2003, 2006) in the clinically unaffected fellow eye.

[1] This chapter has been adapted from the published paper by Ho, C.S. & Giaschi, D.E. (2006). Deficient maximum motion displacement in amblyopia. *Vision Research, 46*, 4595-4603.

Previously, we investigated performance on global motion, motion-defined form, and maximum motion displacement (Dmax) tasks in the fellow eyes of children with amblyopia (Ho et al., 2005). Motion-defined form perception was abnormal in the amblyopic group relative to an age-matched control group. Dmax was abnormal in some children with amblyopia; global motion perception was normal in most children. In that study, only the fellow eyes were tested and the stimulus used to measure Dmax was a dense display comprised of small dots. Dmax, however, is highly dependent on the stimulus parameters chosen and may be determined by either spatial-frequency-dependent (low-level) or feature-matching (high-level) motion mechanisms, depending on the stimulus (Nishida and Sato, 1995; Sato, 1998; Snowden & Braddick, 1990).

Dmax increases with an increase in retinal eccentricity or stimulus size (Baker & Braddick, 1982; Braddick, 1974; Chang & Julesz, 1983a; Nakayama & Silverman, 1984; Todd & Norman, 1995), increase in dot size beyond 15 min (Cavanagh, Boeglin & Favreau, 1985; Morgan, 1992; Sato, 1990), decrease in dot density (Boulton & Baker, 1993; Eagle & Rogers, 1996, 1997; Ramachandran & Anstis, 1983), and/or increase in the number of frames in the random dot kinematogram (RDK) (Nakayama & Silverman, 1984; Nishida & Sato; 1992; Snowden & Braddick, 1989a, b; Todd & Norman, 1995). Dmax also increases with low- or band-pass spatial -frequency filtering that eliminates high spatial frequencies from the stimulus (Chang & Julesz, 1983b; Cleary & Braddick, 1990; De Bruyn & Orban, 1989). Overall, Dmax increases with manipulations that reduce the complexity of the stimulus, and presumably increase the reliance on higher-level feature-matching mechanisms (Sato, 1998).

The stimulus used in our previous study (Ho et al., 2005) would likely be processed by a low-level mechanism. Recent studies on amblyopia, however, suggest that high-level motion processing is more impaired than low-level motion processing (Ho et al., 2006; Simmers et al., 2005, 2006). Our aim with the current study was to investigate the effects of stimulus manipulations on Dmax in amblyopic children, and to compare performance in amblyopic and fellow eyes. Most studies investigate Dmax using 2-frame RDKs that may have less in common with true smooth motion than multi-frame RDKs (De Bruyn & Orban, 1989). We used large field 4-frame RDKs to determine

whether the increase in Dmax typically observed by increasing dot size or reducing dot probability also holds true for children with amblyopia. We determined Dmax for a baseline condition, a reduced dot probability condition, and an increased dot size condition. Dot sizes were selected to fall in a range above 20 min, below which changes in dot size have little effect on Dmax (Cavanagh et al., 1985; Morgan, 1992; Sato, 1990)[2]. Based on previous studies, it is likely that the baseline condition involves low-level processing mechanisms, and the reduced dot probability and increased dot size conditions involve high-level processing mechanisms to a greater extent, which accounts for the observed increase in Dmax with these stimulus manipulations. Throughout this thesis, I refer to the RDKs as low-level and high-level motion stimuli based on these previous characterizations.

The high-level motion system is also hypothesized to exhibit an effect of stimulus onset asynchrony (SOA) consistent with Korte's third law (Sato, 1998) which states that Dmax increases as SOA increases (Korte, 1915). We, therefore, measured Dmax for each of the three conditions at three different SOAs in order to explore high-level motion mechanism involvement. Throughout this study, we refer to low-level mechanisms as spatial-frequency-dependent and high-level mechanisms as feature-matching (Nishida and Sato, 1995; Sato, 1998). To clarify, this distinction differs from the stimulus-based mechanisms used by Cavanagh and Mather (1990). They describe low-level and high-level mechanisms as those involved with first-order stimuli (luminance- or color-defined) and second-order stimuli (motion- or stereo-defined), respectively. The former definition is most appropriate for this study as all motion stimuli used were first-order.

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[2] The spatial frequency content of a random dot pattern is determined by dot size (Julesz, 1971). Altering dot probability without changing dot size does not alter spatial frequency content but reduces the overall power (energy) of the global frequency distribution which is essentially low pass with a cut-off equal to the reciprocal of the dot size (i.e. the sampling interval). Dot density of a random dot pattern can be reduced in several ways: decreasing dot probability, increasing dot size (sampling interval), or low-pass filtering (Eagle & Rogers, 1996). Each of these changes to a random dot pattern has a different effect on the cut-off and amplitude (power) of the global frequency distribution of that pattern: decreasing power in the first case, and decreasing the low-pass cut off in the latter two cases described above. In our experiments, we are manipulating dot density by decreasing dot probability in Condition 2 and increasing dot size for Condition 3, relative to the baseline condition (Condition 1).

## 2.2 METHODS

### 2.2.1 Subject Selection

To rule out potential confounds related to maturation of performance on the Dmax task, all children included in this study were over the age of 8 years. Dmax for dense displays of small dots has been shown to mature at around age 7 to 8 years (Parrish, Giaschi, Boden & Dougherty, 2005).

#### *Control Group*

A total of 18 control children were tested, ranging in age from 9 to 15 years. Eighteen children participated in Experiment 1, and 9 of these children participated in Experiment 2. Distance line VA was measured using the Regan 96% contrast letter chart and near VA was measured using the University of Waterloo near vision test card. The Regan 96% contrast letter chart was used to measure VA because it has letter spacing designed to minimize crowding effects and has a logarithmic progression of letter size (Regan, 1988). All children included had distance and near monocular line visual acuity (VA) equivalent to or better than, respectively, 6/6 or 0.4 M (Jose & Atcherson, 1977). Both acuity cut-off values represent letter size with detail of 1 min when measured at 6m and 40cm, respectively. Stereoacuity was required to be equivalent to or better than 40 sec of arc. Stereoacuity was assessed using the Randot Stereotest (Stereo Optical Co., Inc.). All subjects had normal contrast sensitivity across a range of spatial frequencies when assessed with the Functional Acuity Contrast Test (Vistech Consultants, Inc.). No subject had a history of ocular pathology or abnormal visual development.

#### *Amblyopic Group*

Specific details for the amblyopic participants are described in Section 2.4.

### 2.2.2 Apparatus

The psychophysical tasks were programmed in Matlab and run on a Macintosh Power G4 computer. The stimuli were displayed on a 17" Sony Trinitron monitor with a resolution of 1024 x 768 (horizontal x vertical) pixels and a refresh rate of 75Hz. Subject responses were collected with a MacGravis gamepad.

### 2.2.3 Stimulus

The visual stimuli for all conditions of the Dmax task consisted of randomly generated patterns of white dots (100 cd/$m^2$) on a black background (5 cd/$m^2$). The viewing distance was 1.0 m. The entire random-dot display subtended a visual angle of 18.3 x 13.6 deg (horizontal x vertical).

Each subject performed the task under three display parameters: 20 min dot size at 5% dot density (Condition 1), 20 min dot size at 0.5% dot density (Condition 2), and 1 deg dot size at 5% dot density (Condition 3). The dot sizes listed above represent the diameter of each round dot in the display. Each RDK consisted of 4 frames and the duration of each frame was varied. Each of the 3 stimulus parameters listed above were presented with 3 different SOA times for each frame corresponding to 4, 8, and 12 screen refreshes, at 75Hz. This resulted in total trial durations of 213, 427, and 640 ms, respectively. No inter-stimulus interval was used. This gave a total of 9 conditions.

### 2.2.4 Procedure

The study was approved by the University of British Columbia's Behavioural Research Ethics Board. All testing was completed in one session that lasted approximately 1 hour. Prescribed optical correction was worn throughout testing for subjects requiring refractive correction. Testing was performed under diffuse illumination with lights directed away from the display screen to prevent glare. The non-tested eye was occluded with an opaque black patch. Test distance was monitored throughout all the experimental trials to ensure that it remained constant. Subject responses were self-paced and subjects were asked to guess the correct response if they were unsure. Feedback was provided for the subjects to motivate and encourage them throughout the trials. The eye that was tested first in each experiment was randomly determined.

For each trial, the random dot display was displaced by a given jump size, upward or downward, at 100% coherence, for four consecutive frames of animation. The task was direction discrimination of the apparent motion. A two-alternative forced-choice (2AFC) paradigm was used, in which the probability of accurately guessing the correct response was 50%.

As the displacement increased, the task of direction discrimination became more difficult. A staircase adjusted the jump size of each trial in every condition tested. All conditions began with a jump size of 0.3 deg that all participants performed with 100% accuracy. This start point was selected, after several pilot experiments, to ensure that jump size never decreased beyond the initial start point and that our Dmax measures were not being confounded with potential measures of minimum displacement (Dmin). Jump size was adjusted such that it increased after two correct responses, and decreased after one incorrect response. The initial jump size step was 1 deg and this was halved after each reversal. The staircase ended after the tenth reversal in jump size or after 50 trial presentations, whichever occurred first. This type of staircase procedure has been used successfully with infants (Swanson & Birch, 1990) and its advantages are discussed in Levitt (1970). Throughout testing, subjects were asked to maintain fixation on a cross in the middle of the screen.

### 2.2.5 Threshold Calculations

Thresholds were determined by fitting a Weibull function to the data for each participant on each of the three tasks, using a maximum-likelihood minimization procedure (Watson, 1979). Threshold was defined as the point of maximum slope on the fitted curve, which occurs at 82% correct in a 2AFC procedure (Strasburger, 2001). A $\chi^2$ test was performed to ensure that threshold estimates were valid by confirming that the Weibull function adequately fit the data for each child.

## 2.3. EXPERIMENT 1

The objectives of this experiment were: 1) to establish normal performance on our psychophysical tasks; 2) to confirm that the stimuli gave the expected increase in Dmax with increased dot size, reduced dot probability and increased SOA.

Eighteen subjects (*M*=12.6 yrs, *SD*=2.0 yrs; males n=8, females n=10) were tested on the 9 counterbalanced conditions in each eye.

### 2.3.1 Results

A three-way repeated measures ANOVA was performed with SOA (53, 107, 160 ms), eye tested (first, second), and condition (1, 2, 3) as the within factors. The interactions of condition x eye x SOA, condition x eye, and eye x SOA were non-significant. The only significant interaction was SOA x condition ($F_{1, 18}$=11.78, $p$=.003). Simple main effect analysis revealed a significant effect of SOA only for Condition 2 ($F_{2, 111}$= 5.50, $p$=.005) and Condition 3 ($F_{2, 111}$=5.42, $p$=.006) but not Condition 1 ($F_{2, 111}$=.73, $p$=.487). The effect size for the significant SOA effects were moderate ($\eta_p^2$=0.09) for both Conditions 2 and 3. Bonferroni adjusted pairwise comparisons of mean Dmax thresholds showed that Dmax thresholds obtained using a SOA of 53 ms ($M$=2.95, $SD$=0.59) significantly differed from that obtained using a SOA of 107 ms ($M$=3.36, $SD$=0.63, $p$<.05) and 160 ms ($M$=3.39, $SD$=0.71, $p$<.05) within Condition 2. Within Condition 3, the same pattern of results was obtained and Dmax thresholds obtained for an SOA of 53 ms ($M$=2.68, $SD$=0.61) significantly differed from that obtained using a SOA of 107 ms ($M$=3.04, $SD$=0.63, $p$<.05) and 160 ms ($M$=3.13, $SD$=0.63, $p$<.01). These means are depicted in Figure 2.1.

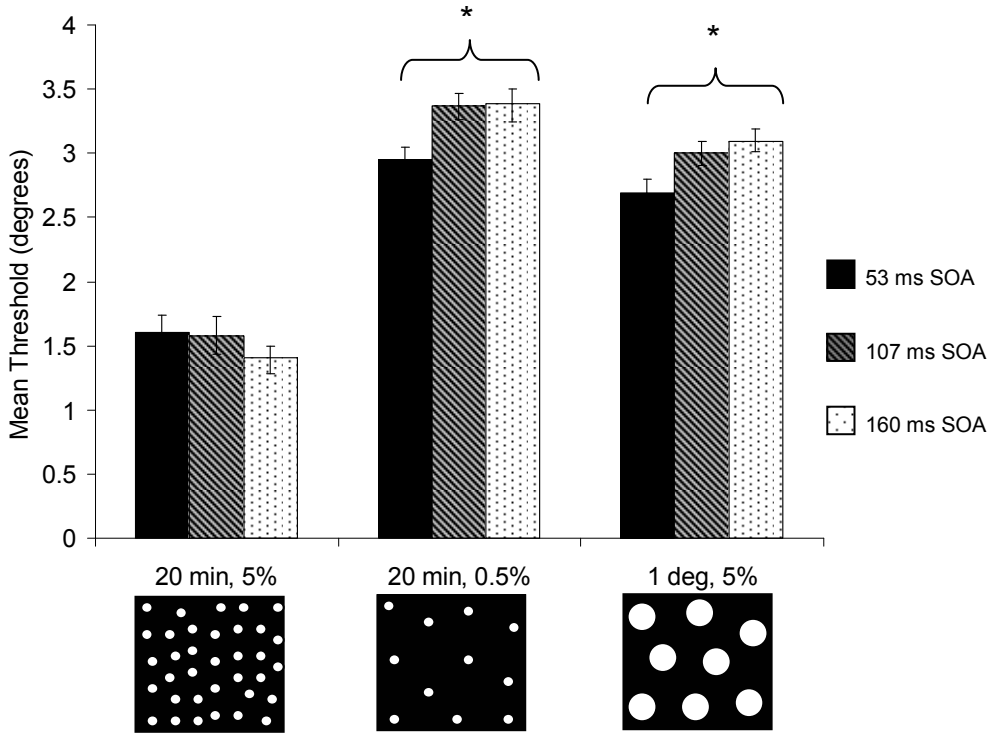


**Figure 2.1:**

Mean Dmax threshold values obtained for the 3 stimulus conditions. The mean threshold represents the displacement that reflected performance with 82% accuracy. The overall mean threshold across both eyes is depicted because the difference between the two eyes was not significantly different. Error bars represent standard errors. A significant difference from the baseline condition (20 min, 5%) is indicated by *. Black, dark gray and light gray bars represent stimulus onset asynchrony (SOA) times of 53, 107, and 160 msec, respectively.

All factors and interactions met the assumption of sphericity with Mauchley's test of sphericity except for the factor of condition. A significant main effect of condition persisted after applying the Greenhouse-Geisser correction ($F_{1.50,\ 27.04}$ = 217.71, $p$=.000). The effect size of the difference was large ($\eta_p^2$=0.92). Bonferroni adjusted pairwise comparisons of mean Dmax thresholds showed that Dmax thresholds obtained for Condition 1 ($M$=1.53, $SD$=0.09) significantly differed from those obtained for

Condition 2 (*M*=3.23, *SD*=0.08, p=.000) and for Condition 3 (*M*=2.95, *SD*=0.07, p=.000). This indicates a significant increase in Dmax with decreased dot probability (Condition 2) and with increased dot size (Condition 3) relative to baseline (Condition 1). Conditions 2 and 3 can not be directly compared as they comprise both different dot densities and dot sizes relative to each other.

As expected, there was no significant main effect of the "eye tested" factor, confirming that performance in the first and second eyes tested was similar. Because both eyes performed similarly, the overall mean thresholds across both eyes are depicted in Figure 2.1.

### 2.3.2 Discussion

Our findings are consistent with previous reports that an increase in Dmax is observed for RDKs with reduced dot probability (Boulton & Baker, 1993; Eagle & Rogers, 1996, 1997; Ramachandran & Anstis, 1983), and increased dot size (Cavanagh et al., 1985; Morgan, 1992; Sato, 1990).

We believe that the larger dot-size and reduced-dot-density conditions represent high-level motion tasks that are mediated by feature-matching mechanisms. Higher-level motion mechanisms give a larger Dmax (Sato, 1998) and in this experiment, both the reduced-dot-density and increased-dot-size conditions gave larger Dmax thresholds than the baseline condition. Furthermore, the effects of SOA in this experiment were statistically significant for only the reduced-dot-probability and the increased-dot-size conditions. Others have reported a similar effect of SOA using displays with increased dot size (Cavanagh et al., 1985; Sato, 1998) and with reduced dot density (Ramachandran & Anstis, 1983; Sato, 1998). A SOA effect is suggestive of high-level, feature-matching mechanisms since low-level spatial-frequency-dependent mechanisms typically do not follow Korte's third law (Sato, 1998).

## 2.4. EXPERIMENT 2

The objective of this experiment was to investigate performance on the above psychophysical Dmax tasks in both eyes of amblyopic children and to compare the obtained thresholds to those of age-matched control children.

The amblyopic group consisted of 9 children ranging in age from 9 to 15 years (*M* = 11.6 yrs, *SD* = 1.8 yrs). The subjects were referred from the Department of Ophthalmology at the Children's and Women's Health Centre of British Columbia, and from other local clinics. The ages and clinical diagnoses of children in the amblyopic group are summarized in Table 2.1. To be included in the amblyopic group, there had to be at least a 1.5 line difference in VA between the amblyopic and fellow eye in the presence of anisometropia and/or strabismus. To be classified as anisometropic in this study, there had to be at least a 1.00 dioptre difference in the spherical equivalent refractive error between amblyopic and fellow eyes. Of the nine subjects, 3 had strabismus and 6 had anisometropia. None of the subjects included had eccentric fixation, latent or manifest nystagmus, anomalous retinal correspondence, or oculomotor dysfunction with the exception of strabismus. Both the amblyopic and fellow eyes were tested. To avoid the possibility of testing subjects with bilateral amblyopia, the inclusion criteria for the fellow eye was the same as that for the control subjects, described above. Four additional amblyopic subjects were excluded from the study for not meeting the inclusion criteria.

**Table 2.1**
Clinical details for amblyopic participants

| Age (years) | Diagnosis | Refractive Error | Ocular Deviation | Decimal VA (fellow eye) | Decimal VA (amblyopic eye) | Stereoacuity |
|---|---|---|---|---|---|---|
| 10.0 | A | R: +3.00+0.75x090<br>L: plano | orthophoria | 1.00 | 0.19 | 50 |
| 10.1 | A | R: +4.00+2.25x085<br>L: +4.00+4.00x100 | 4Δ esophoria | 1.16 | 0.89 | 50 |
| 11.4 | A | R: plano<br>L: +3.25 | orthophoria | 1.03 | 0.73 | 20 |
| 13.0 | A | R: +6.00+0.50x090<br>L: +5.00 | orthophoria | 1.19 | 0.55 | 40 |
| 13.8 | A | R: +3.50+2.00x010<br>L: +4.25+2.75x180 | 2Δ exophoria | 1.00 | 0.46 | 70 |
| 14.9 | A | R: +2.25+2.75x002<br>L: +2.00+1.50x175 | orthophoria | 1.00 | 0.71 | 50 |
| 10.2 | A+S | R: +1.25<br>L: +3.25 | 10Δ esotropia | 1.15 | 0.73 | 500 |
| 10.4* | A+S | R: plano<br>L: +3.25 | 8Δ exotropia | 1.25 | 0.20 | 500 |
| 10.3 | S | R: +0.50<br>L: +0.25 | 4Δ hypertropia &<br>6Δ exotropia | 1.25 | 0.80 | 500 |

A: anisometropic amblyopia S: strabismic amblyopia A+S: aniso-strabismic amblyopia

All subjects with strabismus had history of surgery except for subject marked *.
All subjects with were treated for a period with full time occlusion therapy except for subject marked *.
Δ = prism dioptre

Nine control children that were age-matched to the amblyopic subjects were tested in both eyes. Details for these children are outlined in Section 2.2.1.

All conditions were counterbalanced and the eye that was tested first was randomly varied. Methods were exactly as described in Section 2.2.

### 2.4.1 Results

A repeated measures ANOVA was performed with SOA (53, 107, 160 ms), eye tested (*amblyopic group*: amblyopic, fellow; *control group*: first, second) and condition (1, 2, 3) as the within factors, and group (amblyopic, control) as the between factor.

All higher-order interactions, and the interactions of eye x group, SOA x group, condition x eye, SOA x eye were non-significant. Significant interactions were: 1) SOA x condition ($F_{4, 64}$=3.09, $p$=.022) and 2) group x condition ($F_{2, 32}$=4.24, $p$=.015). Simple main effect analysis of the first significant interaction revealed a significant effect of SOA only for Condition 2 ($F_{2, 102}$= 3.11, $p$=.049), but not Condition 1 ($F_{2, 102}$=1.75, $p$=.180) or Condition 3 ($F_{2, 102}$=1.96, p=.146). The effect size for the significant SOA effect for Condition 2 was moderate ($\eta_p^2$=0.06). Bonferroni adjusted pairwise comparisons of mean Dmax thresholds showed that Dmax thresholds obtained using a SOA of 53 ms ($M$=2.93, $SD$=0.57) significantly differed from that obtained using a SOA of 107 ms ($M$=3.26, $SD$=0.63 $p$<.05) and 160 ms ($M$=3.17, $SD$=0.60, $p$<.10) within Condition 2. The Dmax thresholds for the two longer SOAs did not significantly differ. A similar increasing trend was seen for Condition 3 (53 ms $M$=2.77, $SD$=0.52; 107 ms $M$=3.00, $SD$=0.64; 160 ms $M$=3.04, $SD$=0.64), although not significant statistically. In contrast, a decreasing trend where Dmax thresholds tended to decrease with increasing SOA was found for Condition 1 (53 ms $M$=1.48, $SD$=0.66; 107 ms $M$=1.37, $SD$=0.64; 160 ms $M$=1.24, $SD$=0.31).

Simple main effect analysis of the second significant interaction revealed a significant effect of group only for Condition 1 ($F_{1, 102}$= 8.79, $p$=.004) and Condition 2 ($F_{2, 102}$=5.63, $p$=.019), but not for Condition 3 ($F_{2, 102}$=0.81, $p$=.371). The effect sizes for the significant group effects of Conditions 1 and 2 were moderate ($\eta_p^2$=0.08 and 0.06,

respectively). Dmax thresholds obtained for the amblyopic group ($M$=1.21, $SD$=0.28) were significantly lower than those for the control group ($M$=1.52, $SD$=0.71) for Condition 1. Similarly for Condition 2, thresholds were lower in the amblyopic group. The means were: amblyopic group $M$=2.99, $SD$=0.54, and control group $M$=3.26, $SD$=0.65.

All within factors and interactions met the assumption of sphericity with the exception of SOA. The main effect of SOA was non-significant after applying the Greenhouse-Geisser correction ($F_{1.43, 22.89}$ = 2.49, $p$=.119). The main effects of group ($F_{1, 16}$ = 6.034, $p$=.015) and condition ($F_{2, 32}$ = 228.93, $p$=.000) were both significant, which was predictable based on the significant interactions summarized above. There was no significant main effect of eye tested ($F_{1, 16}$ = 0.02, $p$=.89), indicating that performance between amblyopic and fellow eyes was comparable. The mean thresholds for each eye of the amblyopic group and the average of both eyes for the control group are depicted in Figure 2.2. The Dmax deficits can not be explained by visual acuity loss because the fellow eyes tested met the same inclusion criteria as control eyes.

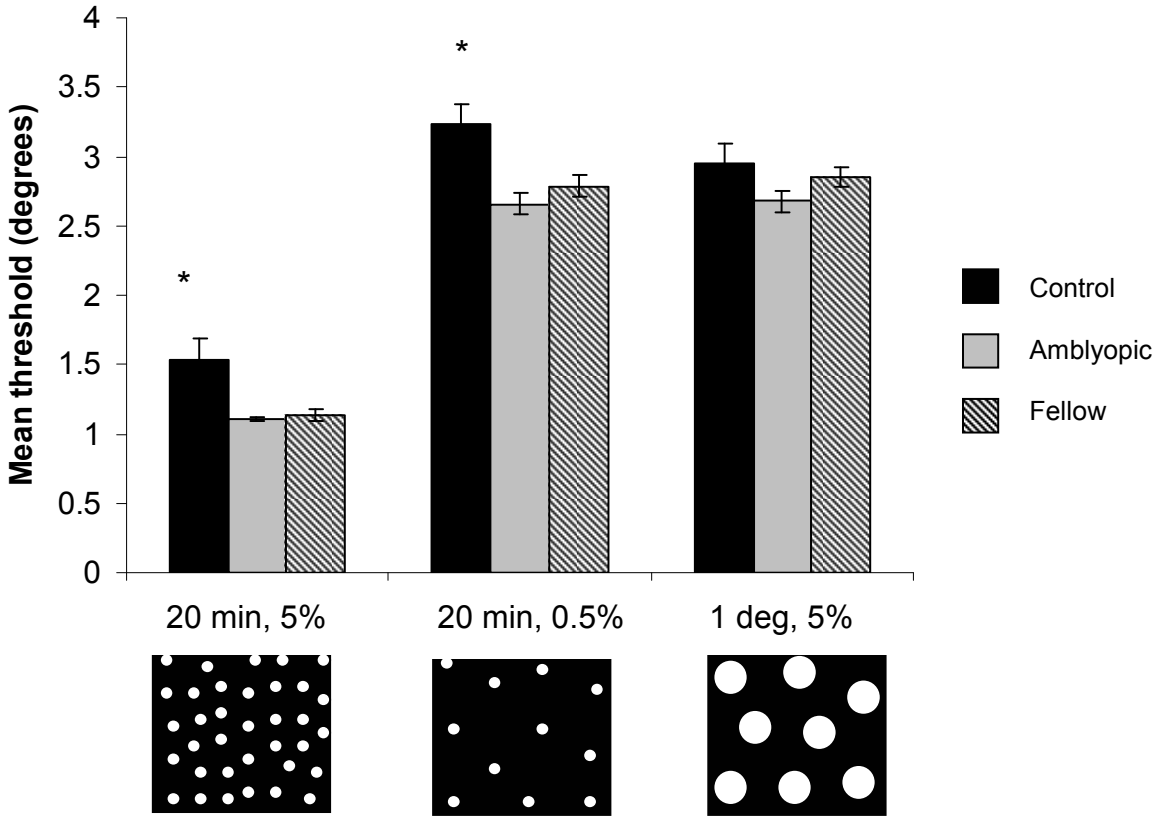


**Figure 2.2:**

Mean Dmax threshold values obtained for the 3 stimulus conditions in control (averaged across both eyes), amblyopic, and fellow eyes. The black, gray and textured bars represent mean Dmax in control, amblyopic, and fellow eyes, respectively. The mean threshold represents the displacement that reflected performance with 82% accuracy. Error bars represent standard errors. A significant difference between the amblyopic and control groups is indicated by *.

McKee and colleagues (McKee, Levi & Movshon, 2003) found that differences in performance on several psychophysical tasks could be predicted based on binocular and non-binocular classifications. We, therefore, classified each amblyopic participant as binocular or non-binocular corresponding to stereoacuity less than or greater than 500 sec, respectively. All 6 participants with pure anisometropia were binocular and the 3 participants with strabismus were non-binocular. Individual z-scores, determined from the means and standard deviations of the control group (for each of the 9 conditions), were used to examine possible Dmax differences between binocular and non-binocular participants. None of the individual z-scores in either eye were > ±1.64, thus the observed deficits in the amblyopic group were not driven by only a few participants with exceptionally abnormal performance. In addition, the negative z-scores, corresponding to lower Dmax thresholds, belonged to both binocular and non-binocular participants, and the deficits appeared to be generalized across all participants with amblyopia. Furthermore, Dmax scores for amblyopic and fellow eyes were not significantly correlated to stereoacuity ($r$ =.03, $p$=.81) suggesting that the reported deficits do not differ based on the degree of binocularity.

### 2.4.2 Discussion

The results suggest that amblyopic children show the expected increase in Dmax for displays with increased dot size or reduced dot density relative to baseline, similar to the controls in Experiments 1 and 2. However, on the baseline and reduced-dot-probability conditions, Dmax was significantly lower in *both* eyes of the amblyopic group compared to the control group. This is illustrated in Figure 2.2. These deficits could reflect a relative immaturity in the amblyopic visual system compared to the age-matched control population.

The conclusion that both low-level (Condition 1) and high-level (Conditions 2 and 3) motion deficits exist in amblyopia can not be clearly made but is suggested by our findings. The results for both Condition 1 and 2 show a significant difference in performance between amblyopic and control groups. Also, Condition 2 does demonstrate the SOA effect that is expected with high-level motion stimuli. The results for Condition 3 do not support this conclusion because neither a significant group nor a SOA effect was found. Dmax for amblyopic and control groups was more similar with

increased-dot-size displays. Further studies involving a range of dot sizes and densities will need to be done to determine the stimulus parameters where control and amblyopic group performance converges.

Several studies have looked at the spatial limits of direction-selective neurons, which can be considered a neural correlate to the psychophysical measure of maximum displacement (Dmax). Mikami and colleagues (Mikami, Newsome & Wurtz, 1986) found that the upper spatial limit of displacement (in the preferred direction) to which direction-selective neurons would respond was three times as large for MT than V1 in alert macaques. The authors concluded that V1 input does not fully account for the directional mechanisms in MT. It is possible that high-level input from extra-striate cortical regions (or low-level input from other direction-selective regions such as V2 or V3) modifies direction-selective responses in MT. In contrast, Churchland and colleagues (Churchland, Priebe & Lisberger, 2005) found that neurons in V1 and MT retained direction selectivity for similar displacement limits, suggesting a strong V1 influence on direction selectivity in MT. Thus, the Dmax deficit in amblyopia could be due to a neural deficit in V1, MT, or other extra-striate regions that provide input to these cortical areas. Regions of the dorsal stream may be among the extra-striate regions involved. Simmers and colleagues reported deficits implicating MT using first- and second- order global motion stimuli (Simmers et al., 2003, 2005) as well as deficits implicating MSTd using translational, rotational, and radial optic flow patterns (Simmers et al., 2006) in an amblyopic population.

There have been reports of high-level, attentive motion perception deficits in individuals with parietal lobe lesions that spare low-level motion perception (Battelli, Cavanagh, Intriligator, Tramo, Henaff, Michel & Barton, 2001; Michel & Henaff, 2004) as well as in amblyopic children (Ho et al., 2006). The attentive-tracking deficits seen in amblyopia (Ho et al., 2006) are likely associated with impairment of the parietal cortex because Culham and colleagues identified parietal activation using similar attentive-tracking tasks with functional MRI (Culham, Brandt, Cavanagh, Kanwisher, Dale & Tootell, 1998). Other groups have also identified significant parietal lobe involvement in high-level motion perception with fMRI (Claeys, Lindsey, De Schutter & Orban, 2003). Attentive tracking (Cavanagh, 1992) is a high-level motion task that involves feature-

matching mechanisms. Attentive tracking and high-level Dmax may share similar or related feature-matching mechanisms.

There is physiological evidence showing that parietal areas in the macaque are involved in high-level motion processing (Assad & Maunsell, 1995) and high-level direction discrimination (Williams, Elfar, Eskandar, Toth & Assad, 2003). Williams and colleagues suggest the role of parietal neurons in motion perception is to fill in gaps when visual information is incomplete or ambiguous. This could be extended to the perception of apparent motion under certain stimulus parameters such as random dot displays with low dot densities and/or large dot size (Sato, 1998), as well as to classical long-range stimuli (Braddick, 1974).

Aspects of form perception/ventral stream processing, however, have also been shown to be active in long-range apparent motion (Zhou et al., 2003). Thus, although there is much evidence suggesting dorsal stream impairment in amblyopia (Simmers et al., 2003, 2006; Ho et al., 2006), ventral stream involvement can not be ruled out in explaining high-level Dmax deficits. Deficits of global orientation, texture-defined form and motion-defined form, for example, suggest ventral stream involvement in amblyopia (Simmers et al., 2005, Wang et al., 2006). A recent neuroimaging study identified reduced activation in primary and secondary visual areas as well as parieto-occipital and ventral temporal cortex in human amblyopia (Anderson & Swettenham, 2006).

## 2.5 GENERAL DISCUSSION

Our findings provide further evidence that motion processing is not normal in amblyopia and that these reported deficits can not be explained fully by an inability to see the motion stimulus due to reduced visual acuity. Cortical regions that are highly binocular are implicated because the deficits are not limited to just amblyopic eyes, but also affect fellow eyes. It is likely that the baseline condition is processed through low-level mechanisms and the reduced-dot-probability and increased-dot-size conditions involve higher-level mechanisms. Sato (1998) discussed the possibility that as dot probability is decreased and dot size is increased, there is a switch from low- to high-level processing

for Dmax. Our results suggest that this "switch" is intact in amblyopia, but that both low-level and high-level motion deficits may exist.

The results of this study can not be completely accounted for by spatial-frequency-dependent mechanisms. The increased Dmax with reduced-dot-probability and larger-dot-size conditions are consistent with results predicted based on feature matching. Because the larger dot-size condition has lower spatial-frequency content, it may involve larger low-level motion detectors that yield a larger Dmax. This can not explain the Dmax increase observed for the reduced-dot-probability condition which does not involve larger detectors than the baseline condition since dot size is constant. Interestingly, Dmax has been shown to increase with reduced dot density (Sato, 1998) and increased dot size (Eagle & Rogers, 1996; Morgan, Perry & Fahle, 1997; Smith & Ledgeway, 2001) even with high-pass filtered stimuli which should eliminate the low-spatial-frequency motion signal and decrease Dmax. High-spatial frequencies appear capable of carrying motion signals, not through low-level mechanisms, but likely through high-level, feature-matching mechanisms (Bex & Dakin, 2003; Eagle, 1998; Glennerster, 1998).

Previously, Ho and colleagues (2005) reported Dmax deficits in the fellow eyes of amblyopic children between the ages of 4 and 11 years of age. A trend was reported for children with anisometropic amblyopia to have abnormally high Dmax and those with strabismic amblyopia to have abnormally low Dmax, relative to control children. The stimulus in this previous study was an 8-frame RDK of 5% dot density and 0.84 min dots. Previous studies have shown that increasing dot size beyond 15 min elevated Dmax, but changes in dot size had little effect on Dmax for dot sizes below 15 min (Cavanagh et al., 1985; Morgan, 1992; Sato, 1990). It would be reasonable to assume that Dmax for the baseline condition in this study should give similar results to the previous study especially since 8 of the 9 amblyopic children tested in this study had anisometropia. However, in the present study, we did not find fellow eye performance to be better than controls for our baseline condition. This can be explained if we consider that most of the children tested in the previous study likely had fewer high spatial-frequency-tuned detectors because they: 1) were not visually mature and 2) were still undergoing occlusion therapy for anisometropic amblyopia. In the current

study, all children had completed occlusion therapy. During occlusion therapy, visual acuity or detection of high-spatial frequencies generally improves. If the number of high-spatial-frequency tuned receptors increases during occlusion therapy, then there may be more high-spatial-frequency masking, at least for the baseline (low-level) condition. This could cause a gradual reduction in Dmax values in both fellow and amblyopic eyes. Once visual maturity is reached, amblyopic children may "lag" behind age-matched controls. For example, lateral connections may be more constrained in amblyopia, limiting the spatial extent of motion detectors, and be manifested as a reduced Dmax.

Future studies investigating changes in Dmax in amblyopic children as they undergo occlusion therapy, using a range of stimulus parameters, as well as functional neuroimaging will help to elaborate upon these current findings.

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# CHAPTER 3: STEREOPSIS-DEPENDENT DEFICITS IN MAXIMUM MOTION DISPLACEMENT IN STRABISMIC AND ANISOMETROPIC AMBLYOPIA[1]

## 3.1 INTRODUCTION

Visual deprivation, ocular misalignment (strabismus) and/or unequal refractive errors (anisometropia) during the critical period of visual development can cause amblyopia. Unilateral amblyopia is characterized by reduced best-corrected visual acuity (VA) in the affected eye and normal VA in the fellow eye.

There is growing evidence that motion perception is impaired in amblyopia. Motion perception defects have been reported in amblyopic eyes (Buckingham, Watkins, Bansal & Bamford, 1991; Ellemberg, Lewis, Maurer, Brar & Brent, 2002; Giaschi, Regan, Kraft & Hong, 1992; Hess, Demanins & Bex, 1997; Ho & Giaschi, 2006; Ho et al., 2005; Ho et al., 2006; Kelly & Buckingham, 1998; Schor & Levi, 1980a, 1980b; Simmers, Ledgeway, Hess & McGraw, 2003; Simmers, Ledgeway, Mansouri, Hutchinson & Hess, 2006; Steinman, Levi & McKee, 1988) and well as in the clinically unaffected fellow eye (Ellemberg et al., 2002; Giaschi et al., 1992; Ho & Giaschi, 2006; Ho et al., 2005, 2006; Kelly & Buckingham, 1998; Simmers et al., 2003, 2006).

Maximum motion displacement (Dmax) is the largest displacement at which the direction of a random-dot kinematogram (RDK) can be reliably discriminated. Dmax may be determined by the receptive field size of low spatial-frequency-tuned motion detectors at a low level of motion processing and/or by the limits of spatial feature matching at high levels of motion processing (Nishida & Sato, 1995; Sato, 1998; Snowden & Braddick, 1990). Sato (1998) has suggested that as dot probability is decreased or dot size is increased, there is a switch from low-level to high-level motion processing of RDKs. Smith and Ledgeway (2001) have suggested that the low- and high-level mechanisms operate (within overlapping ranges) simultaneously rather than

[1] This chapter has been adapted from the published paper by Ho, C.S. & Giaschi, D.E. (2007). Stereopsis-dependent deficits in maximum motion displacement in strabismic and anisometropic amblyopia. *Vision Research, 47*, 2778-2785.

separately. The mechanism that predominates depends largely on stimulus parameters. Dmax increases with reduced dot density (Sato, 1998) and increased dot size (Eagle & Rogers, 1996; Morgan, Perry & Fahle, 1997; Smith & Ledgeway, 2001) to a value that surpasses the receptive field limits of low-level motion detectors. This increase in Dmax with reduced dot density and increased dot size persists even when RDKs are high-pass filtered (which reduces activity in low-level motion detectors with larger receptive fields). In the absence of low spatial frequencies, high spatial frequencies presumably carry motion signals through high-level, feature-matching mechanisms (Bex & Dakin, 2003; Eagle, 1998; Glennerster, 1998).

Previously we reported deficits in Dmax (Ho & Giaschi, 2006) in a group of amblyopic children with mixed etiologies. The children with amblyopia showed the expected increase in Dmax with increased dot size and reduced dot probability. Although the "switch" from low- to high-level mechanisms was present, amblyopic children demonstrated lower Dmax, relative to age-matched control children, for RDKs biased toward low-level or toward high-level motion systems.

In this study, we elaborate upon these findings. We modified the RDK conditions used previously (Ho & Giaschi, 2006) by applying a high-pass filter to the stimuli. Eliminating low spatial frequencies from the stimulus enables us to bias the high-level motion system to a greater extent. Removing low spatial frequencies should impair the low-level motion system but not influence the feature matching capabilities of the high-level motion system. The high-level motion system, but not the low-level system, exhibits an effect of stimulus onset asynchrony (SOA) consistent with Korte's third law such that Dmax increases with increasing SOA (Korte, 1915). To confirm that high-pass filtering targeted high-level mechanisms, we looked for the presence of an SOA effect such that Dmax increases with increasing SOA. We expected that high-pass filtering would decrease Dmax relative to the unfiltered version of the same RDKs, because the combined motion signal from the sum of outputs from low- and high-level motion mechanisms would be less.

Recent studies have suggested a greater impairment of high-level motion processing than low-level motion processing in amblyopia (Ho et al., 2006; Simmers, Ledgeway &

Hess, 2005; Simmers et al., 2003, 2006). Our previous Dmax study (Ho & Giaschi, 2006) looked at a mixed group of amblyopic children. Past studies have found psychophysical deficits of spatial vision to differ between individuals with anisometropic and strabismic amblyopia (Birch & Swanson, 2000; Levi, 1991 (review)). The aim of this study was to investigate whether any differences exist in high-level motion processing (using Dmax) between anisometropic and strabismic amblyopia. The results suggest a relationship between correspondence mechanisms involved in feature matching and stereopsis in amblyopia.

## 3.2 METHODS

### 3.2.1 Subject Selection

Dmax for dense displays of small dots has been shown to mature at around age 7 to 8 years (Parrish, Giaschi, Boden & Dougherty, 2005). All children included in the present study were over the age of 8 years to avoid potential confounds related to maturation on the Dmax task.

#### *Control Participants*

A total of 6 control children were tested, ranging in age from 9 to 15 years (*M* = 12.7 yrs, *SD* = 1.4 yrs). All children included had distance and near monocular line visual acuity (VA) equivalent to or better than 6/6 or 0.4 M, respectively (Jose & Atcherson, 1977). Both acuity cut-off values represent letter size with detail of 1 min when measured at 6m and 40cm, respectively. Distance line VA was measured using the Regan 96% contrast letter chart and near VA was measured using the University of Waterloo near vision test card. Stereoacuity, assessed using the Randot Stereotest (Stereo Optical Co., Inc.), was required to be equivalent to or better than 40 sec of arc. Worth 4 Dot testing (reviewed in Rutstein & Daum, 1998) was used to test for fusion and scored to give another measure of binocularity. The scoring was as follows:

5 = constant fusion
4 = intermittent fusion with intermittent diplopia
3 = constant diplopia
2 = intermittent suppression

1= constant suppression

All control subjects, when tested in the dark, were required to have a score of 5 when tested at 1 m (the test distance used for the experiment). No control subject had a history of ocular pathology or abnormal visual development.

***Amblyopic Participants***

The subjects were referred from the Department of Ophthalmology at the Children's and Women's Health Centre of British Columbia, and from other local clinics. The age range of the children tested was between 9 and 15 years. The ages and clinical details of the amblyopic children are summarized in Table 3.1. Data were collected from 6 amblyopic children with strabismus (*M* = 13.0 yrs, *SD* = 2.1 yrs) and 6 with anisometropia (*M* = 12.5 yrs, *SD* = 1.6 yrs). To be included in the amblyopic group, there had to be at least a 1 line difference in VA between the amblyopic and fellow eye in the presence of anisometropia and/or strabismus. To be classified as anisometropic in this study, there had to be at least a 1.00 dioptre difference in the spherical equivalent refractive error between amblyopic and fellow eyes. None of the subjects included had eccentric fixation, latent or manifest nystagmus, anomalous retinal correspondence, or oculomotor dysfunction with the exception of strabismus. Only 2 subjects (both with strabismus) had not undergone patching. Only one of the strabismic participants tested had congenital esotropia; all others had later onset strabismus. Both the amblyopic and fellow eyes were tested. To avoid the possibility of testing subjects with bilateral amblyopia, the inclusion criteria for the fellow eye was the same as that for the control subjects, described above. One additional amblyopic subject with strabismus was excluded from the study for not meeting the inclusion criteria. To be included in the strabismic group, the ocular deviation needed to be present on unilateral cover testing.

Although 3 of the 6 strabismic children also had anisometropia, they were included in the strabismic subgroup. Psychophysically classifying aniso-strabismic individuals into "strabismic amblyopia" is not infrequent (e.g. Barnes, Hess, Dumoulin, Achtman & Pike, 2001; Demanins, Wang & Hess, 1999; Mansouri, Allen & Hess, 2005; Mussap & Levi, 1999). Children with strabismus, regardless of the age of onset or the concurrent presence of anisometropia, demonstrate different spatial deficits than children with pure

anisometropia (Birch & Swanson, 2000). In this study, children with stereoacuity <500 sec were considered binocular and those with no measurable stereoacuity (>500 sec) on the Randot Stereotest were considered non-binocular. In general, the anisometropic and strabismic groups were considered to represent binocular and non-binocular groups, respectively. The average stereoacuity and Worth-4-Dot scores for the anisometropic group in this study were 33 sec (*SD*=12.1) and 4.7 (*SD*=0.52). The same scores in the strabismic group were 387 sec (*SD*=185) and 1.8 (*SD*=0.98).

## Table 3.1: Clinical details for amblyopic participants

| | Age | logMAR VA (ambyopic) | Decimal VA (amblyopic) | LogMAR VA (fellow) | Decimal VA (fellow) | Stereoacuity (sec of arc) | Worth-4-Dot | Refraction | Clinical Details & Ocular Deviation |
|---|---|---|---|---|---|---|---|---|---|
| **A** | 10.0 | 0.05 | 0.89 | -0.06 | 1.15 | 50 | 4 | OD:+4.00+2.50x85<br>OS:+3.75+4.00x11 | Diagnosed age 3; patching; 4Δ esophoria |
| **A** | 11.2 | 0.14 | 0.73 | -0.01 | 1.03 | 20 | 5 | OD:-1.50<br>OS:plano | Diagnosed age 5; patching; orthophoria |
| **A** | 12.8 | 0.26 | 0.55 | -0.08 | 1.19 | 40 | 5 | OD:+6.00+0.50x90<br>OS:+5.50 | Diagnosed age 2; patching; 2Δ esophoria |
| **A** | 13.0 | 0.15 | 0.71 | 0.00 | 1.00 | 20 | 5 | OD:+0.25+0.50x63<br>OS:-2.00 | Diagnosed age 3; patching; 8Δ exophoria |
| **A** | 13.8 | 0.06 | 0.87 | 0.00 | 1.00 | 40 | 5 | n/a | Diagnosed age 5; patching; orthophoria |
| **A** | 14.1 | 0.16 | 0.69 | 0.03 | 0.94 | 30 | 4 | OD:+2.00+1.50x77<br>OS:+2.25+2.50x92 | Diagnosed age 11; patching; 4Δ esophoria |
| **S+A** | 10.2 | 0.36 | 0.43 | -0.10 | 1.26 | >500 | 1 | OD:plano<br>OS:+3.25 | Diagnosed age 10; no treatment; 8Δ LXT |
| **S+A** | 10.7 | 0.24 | 0.58 | -0.09 | 1.22 | >500 | 1 | OD:+5.00<br>OS:+3.50 | Diagnosed age 6; no surgery; patching; 12Δ RET |
| **S** | 13.6 | -0.04 | 1.09 | -0.10 | 1.26 | 70 | 3 | OD:plano<br>OS:plano | Diagnosed age 3; no surgery; patching; 15Δ LXT |
| **S** | 13.6 | -0.04 | 1.09 | -0.09 | 1.22 | >500 | 3 | OD:plano<br>OS:plano | Diagnosed age 9 mo; surgery; no patching; 6Δ RET |
| **S+A** | 14.7 | 0.25 | 0.56 | 0.04 | 0.92 | 250 | 2 | OD:-0.75+1.00x90<br>OS:-4.75+3.00x80 | Diagnosed age 7; no surgery; non-compliant patching; 15Δ LXT |
| **S** | 15.3 | 0.35 | 0.45 | -0.16 | 1.45 | >500 | 1 | OD:plano<br>OS:plano | Diagnosed age 4; patching; 12Δ RET |

**A**=anisometropia; **S**=strabismus; **RET**=right esotropia; **LXT**: left exotropia; **Δ**=prism dioptre

### 3.2.2 Apparatus

The psychophysical tasks were programmed in Matlab and run on a Macintosh Power G4 computer. The stimuli were displayed on a 17" Sony Trinitron monitor with a resolution of 1024 x 768 (horizontal x vertical) pixels and a refresh rate of 75Hz. Subject responses were collected with a Gravis Gamepad Pro.

### 3.2.3 Stimulus

The visual stimuli for all conditions of the Dmax task consisted of randomly generated patterns of white dots (100 cd/$m^2$) on a black background (5 cd/$m^2$). The viewing distance was 1.0 m. The entire random-dot display subtended a visual angle of 18.3 x 13.6 deg (horizontal x vertical).

Each subject performed the task under three display parameters: 20 min dot size at 5% dot density (condition 1 = baseline condition), 20 min dot size at 0.5% dot density (condition 2 = reduced dot probability condition), and 1 deg dot size at 5% dot density (condition 3 = increased dot size condition). The dot sizes listed above represent the diameter of each round dot in the display. Each RDK consisted of 4 frames and the duration of each frame was varied. Each of the 3 conditions was presented with 2 different SOA times for each frame corresponding to 4 (53 ms) and 12 (160ms) screen refreshes, at 75Hz. This resulted in total trial durations of 213 and 640 ms, respectively. No inter-stimulus interval was used. The above six conditions were repeated with the dots passed through a $5^{th}$ order (sharp cut-off) high-pass Butterworth filter with a cut-off spatial frequency at 1.5c/deg. This eliminated all spatial frequencies in the display that were below 1.5c/deg (corresponds to 20 min of arc). In theory, this cut-off would eliminate any detail larger than 20 min of arc from the display which includes the spatial frequency content of the large 1 deg dots, and the smaller 20 min dots. This resulted in 6 unfiltered and 6 filtered conditions. Each subject completed all 12 conditions with order counterbalanced across subjects.

### 3.2.4 Procedure

The study was approved by the University of British Columbia's Behavioural Research Ethics Board. All testing was completed in two sessions that lasted approximately 1 hour each. Prescribed optical correction was worn throughout testing for subjects

requiring refractive correction. Testing was performed under diffuse illumination with lights directed away from the display screen to prevent glare. The non-tested eye was occluded with an opaque black patch. Test distance was monitored throughout all the experimental trials to ensure that it remained constant. Trial presentation and subject responses were self-paced and subjects were asked to guess the correct response if they were unsure. Feedback was provided for the subjects throughout the trials. The eye to be tested in the first session was randomly determined for all control and amblyopic subjects. The eye tested at the second session was done so using a different counterbalanced order of conditions than that used in the first session.

For each trial, the random dot display was displaced by a given jump size, upward or downward, at 100% coherence, for four consecutive frames of animation. The task was direction discrimination of the apparent motion. A two-alternative forced-choice (2AFC) paradigm was used, in which the probability of accurately guessing the correct response was 50%.

As the displacement increased, the task of direction discrimination became more difficult. For each of the 12 conditions, six displacement levels were presented: 0.3, 1.3, 2.3, 3.3, 4.3 and 5.3 deg. The levels were chosen based on previous findings (Ho & Giaschi, 2006) and additional pilot testing with the filtered displays. Each displacement level was presented 20 times in random order, according to the method of constant stimuli. To ensure that the task was understood before each session, the participants completed a practice run where each displacement level was presented 5 times using displays in which the dot size, dot density and filtered state were randomly varied. Throughout testing, subjects were asked to maintain fixation on a cross in the middle of the screen.

### 3.2.5 Threshold Calculations

Psychometric functions were fitted using the Psignifit toolbox version 2.5.41 for Matlab (see http://bootstrap-software.org/psignifit/) which implements the maximum-likelihood method described by Wichmann and Hill (2001). Dmax was defined as the stimulus level at which performance was 75% correct, halfway between the guess rate (50% correct) and perfect performance (100% correct) for a 2AFC paradigm.

### 3.3 RESULTS

A repeated measures ANOVA was performed with SOA (53, 160 ms), eye tested (*amblyopic group*: amblyopic, fellow; *control group*: first, second), condition (1 - baseline, 2 – reduced dot probability, 3 – increased dot size), and filtered state (no filter, high-pass filter) as the within factors, and group (amblyopic, control) as the between factor.

No Greenhouse-Geisser correction was required. All reported significance values are for data with sphericity assumed because Mauchley's test of sphericity was non-significant for all within factors and for all interactions. Higher-order interactions were non-significant as were the two-way interactions of eye x group ($p$=.72), SOA x group ($p$=.84), condition x group ($p$=.48), filter x group ($p$=.87), condition x eye ($p$=.44), filter x eye ($p$=.34), SOA x eye ($p$=.87), condition x filter ($p$=.11), condition x SOA ($p$=.81), and filter x SOA ($p$=.21).

The main effects of the between factor, group ($F_{1, 15}$ = 7.11, $p$=.017), and within factors of condition ($F_{2, 30}$ = 108.9, $p$=.000), SOA ($F_{1, 15}$ = 8.36, $p$=.011) and filtered state ($F_{1, 15}$ = 8.01, $p$=.013) were all significant. There was no significant main effect of eye tested ($F_{1, 15}$ = 0.23, $p$=.641), indicating that performance between amblyopic and fellow eyes was comparable. The effect sizes for the group ($\eta_p^2$ =.022) and eye ($\eta_p^2$ =.015) mean differences were small. The effect sizes for the condition ($\eta_p^2$ =.88), filtered state ($\eta_p^2$ =.35), and SOA ($\eta_p^2$ =.36) mean differences were large (Cohen, 1992).

Figure 3.1 illustrates mean Dmax values for control, anisometropic, and strabismic groups. Post-hoc analyses of significant main effects with more than two levels (condition and group) were done. Bonferroni adjusted pairwise comparisons showed that Dmax obtained for condition 1 ($M$=1.95, $SD$=0.93) significantly differed from that obtained for condition 2 ($M$=3.62, $SD$=1.05, $p$=.00) and condition 3 ($M$=3.54, $SD$=0.89, $p$=.00). Dmax differences between condition 2 and 3 are not important since the two conditions have neither dot size nor dot density in common ($p$=1.00). Bonferroni adjusted pairwise comparisons showed that Dmax obtained for the control group ($M$=3.22, $SD$=0.92) significantly differed from that obtained for the strabismic group

(*M*=2.88, *SD*=1.43, *p*=.014) and, to a lesser degree, for the anisometropic group (*M*=3.01, *SD*=1.28, *p*=.083). The anisometropic and strabismic group thresholds did not significantly differ from each other (*p*=0.27) (see Figure 3.1).

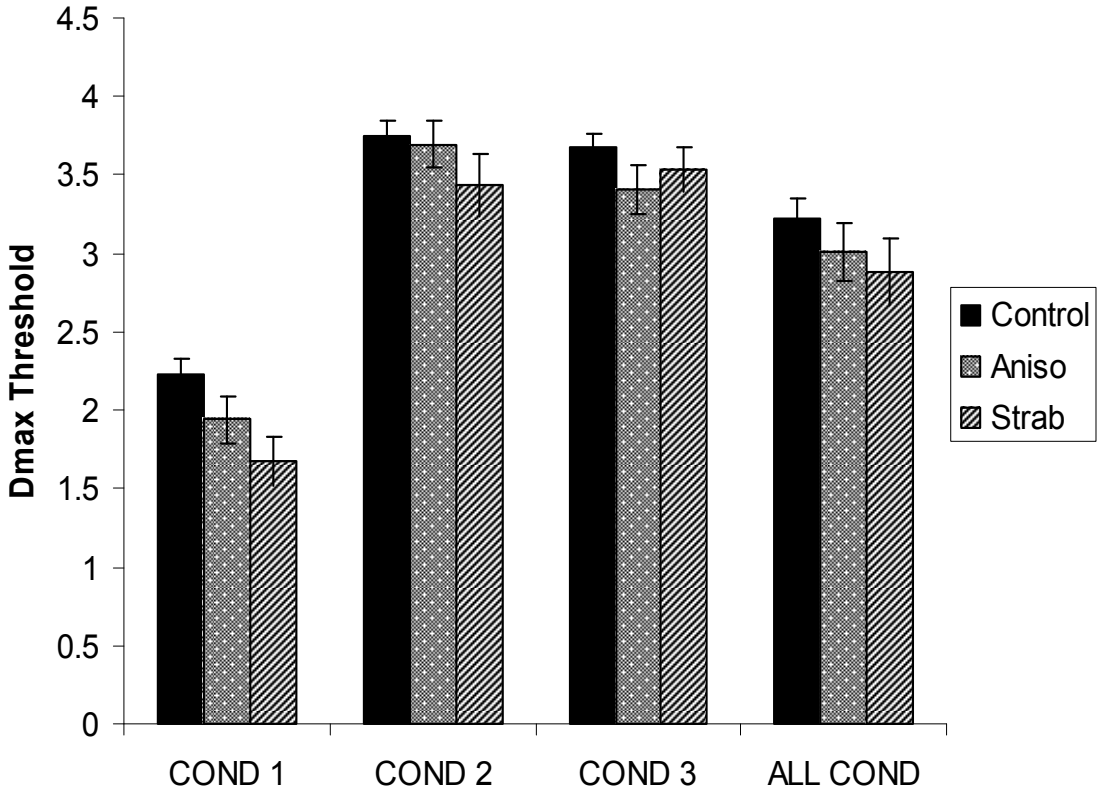


**Figure 3.1**

Mean Dmax values obtained for the 3 stimulus conditions in control, anisometropic, and strabismic groups (averaged across both eyes, both filtered states and both SOAs). Error bars represent standard errors. The fourth data group represents Dmax averaged across all conditions, eyes, SOAs, and filtered states.

Figure 3.2 depicts the SOA effect obtained for each condition in each of the 3 groups (averaged across both eyes). In general, an effect of SOA was identified consistently for all conditions with the exception of condition 1, the low level condition. This was

predictable since the non-filtered (low-level) and high-pass filtered (high-level) versions of condition 1 give opposite SOA effects. In contrast, the increase in Dmax was expected as SOA increased for both the non-filtered and the high-pass filtered versions of conditions 2 and 3 (all high-level).

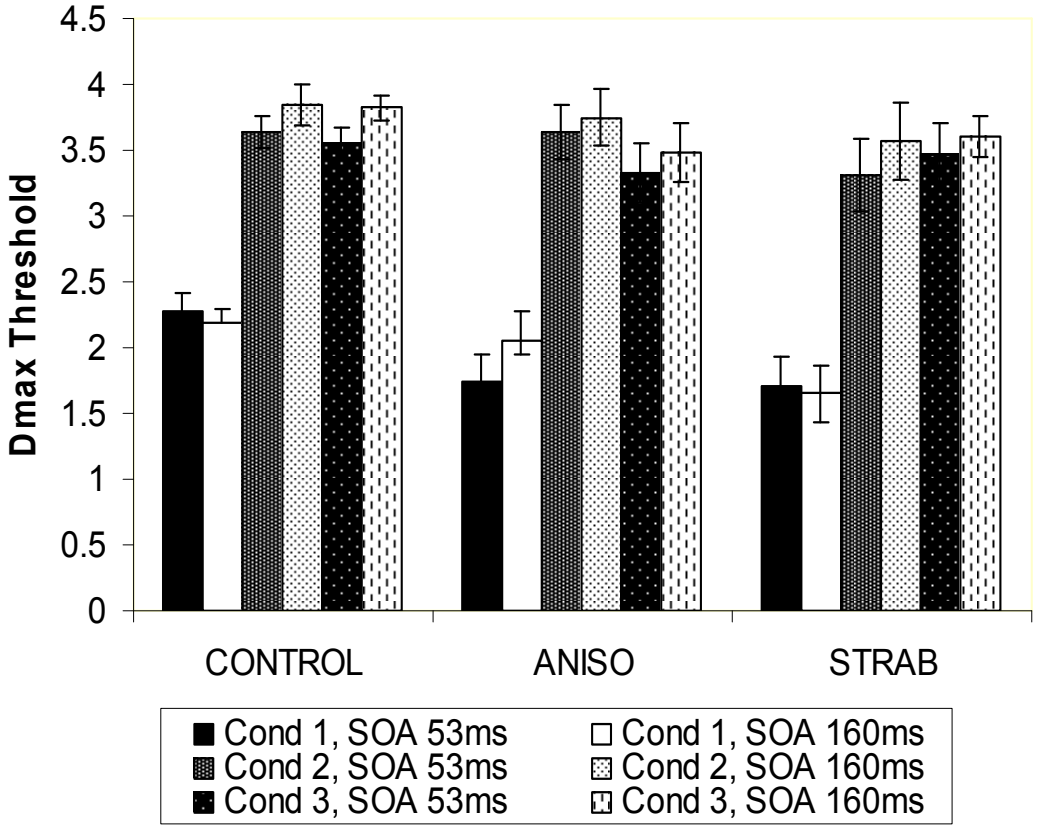


**Figure 3.2:**

Mean Dmax values obtained for the 3 stimulus conditions in control, anisometropic, and strabismic groups (averaged across both eyes). The values depicted represent an average of both filtered states. Darker bars represent average thresholds, in each condition, when tested with a 53ms SOA. Lighter bars represent the average thresholds with a 160ms SOA. Error bars represent standard errors.

Figure 3.3 depicts mean Dmax values (averaged across both eyes) for the non-filtered and high-pass-filtered RDKs in each of the 3 groups. In general, high-pass filtering gave the expected reduction in Dmax for all three conditions.

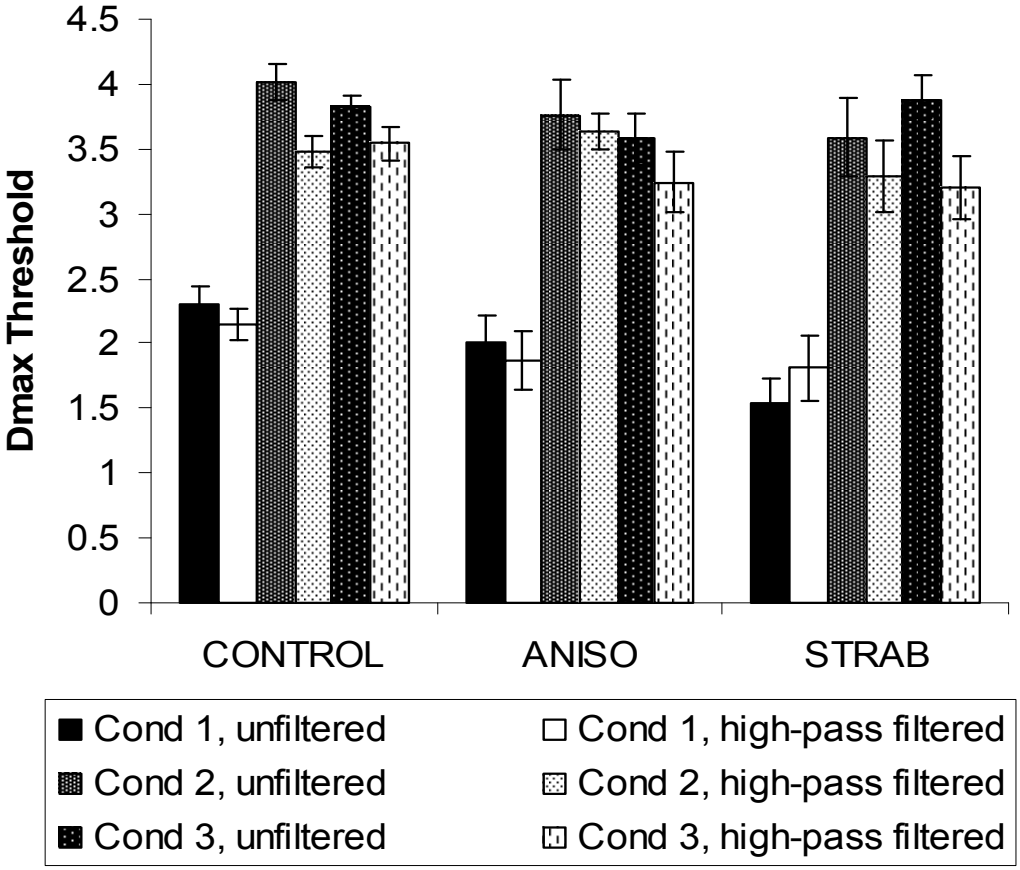


**Figure 3.3:**

Mean Dmax values obtained for the 3 stimulus conditions in control, anisometropic, and strabismic groups (averaged across both eyes). The values depicted represent an average of 53ms and 160ms SOAs. Darker bars represent Dmax for stimuli without filtering. Lighter bars represent Dmax with high-pass filtered stimuli. Error bars represent standard errors.

Correlations between Dmax and age, amblyopic eye logMAR VA (AVA), fellow eye logMAR VA (FVA), stereoacuity, and W4D scores were tested. Using all anisometropic data (N=144), a moderate correlation was found between stereoacuity and Dmax ($r$ =0.34). The correlation to stereoacuity was slightly stronger for Dmax obtained with high-pass filtered (N=72, $r$ =0.40) compared to non-filtered stimuli (N=72, $r$ =0.32). This suggests that overall Dmax in the anisometropic group was higher when stereoacuity

was worse and slightly more so when the RDK was high-pass filtered. Because the data involve repeated measures, conclusions based on inferential statistical analysis of the correlations can not be reliably made.

A similar trend was found in the strabismic group. Using all strabismic data (N=144), a moderate correlation was found between stereoacuity and Dmax ($r$ =0.45) and FVA ($r$ =-0.25). The correlation to stereoacuity was especially robust for Dmax scores obtained with high-pass filtered (N=72, $r$ =0.62) compared to non-filtered stimuli (N=72, $r$ =0.29). The reverse trend was true for the FVA, which was found to be greater for the non-filtered data (N=72, $r$ =-0.35) than the filtered data (N=72, $r$ =-0.14). In the strabismic group, performance on the Dmax task tended to be higher when stereoacuity was worse (more so for the high-pass filtered conditions), and when FVA was better (for the non-filtered conditions only). The finding of larger Dmax with reduced stereoacuity maybe related to the previous report of significantly better global motion thresholds when stereoacuity was reduced (Ho et al., 2005).

### 3.4 DISCUSSION

These results confirm that amblyopic children have lower Dmax overall than control children, for RDKs biased toward either low-level or high-level mechanisms. Both eyes tested had similar Dmax thresholds consistent with the findings previously reported (Ho & Giaschi, 2006). Because the fellow eyes tested met the same inclusion criteria as control eyes, Dmax deficits are not likely explained by visual acuity loss. As expected, the high-pass filtered conditions of the RDKs yielded lower Dmax than their respective unfiltered conditions. In all groups, reduced dot probability and increased dot size conditions gave higher Dmax. Smith & Ledgeway (2001) have suggested that for all motion stimuli, both mechanisms are active however the most efficient one (low- or high-level) predominates. We did show a reduction in Dmax for conditions 2 and 3 with high-pass filtering (Figure 3.2) but Dmax is still significantly greater than that obtained for condition 1 in both the filtered and non-filtered states. This suggests that there is low-level involvement for the latter 2 conditions but that high-level mechanisms still predominate. The increase in Dmax with conditions 2 and 3, relative to condition 1, can not be explained solely by the receptive field size of low-level motion detectors.

Although strabismic children had lower Dmax than anisometropic children, there was no significant difference in performance between the two amblyopic groups. Recent fMRI studies did not find a difference in activation at higher visual areas between strabismic and anisometropic amblyopia (Muckli et al., 2006; Lerner et al., 2003, 2006). The general trend was for the extent of deficits to increase progressively from lower visual areas to higher visual areas.

A relationship between stereoacuity and Dmax was found in both anisometropic and strabismic groups of children. In both groups, as stereoacuity got worse, Dmax increased. The strength of correlation was greatest within the strabismic group and most noticeable for the high-level (high-pass filtered) conditions in both groups.

This is not the first report of reduced visual processing deficits in individuals with poor stereoacuity relative to those with better stereoacuity. For instance, slow monocular global motion thresholds (Ho et al., 2005), monocular contrast sensitivity thresholds (McKee, Levi & Movshon, 2003) and intraocular transfer of global motion stimuli (McColl & Mitchell, 1998) have been found to be better or spared in individuals with no measurable stereoacuity relative to those with measurable stereoacuity. Strabismic individuals with reduced stereopsis demonstrate an exaggeration of the fine grain motion illusion (FGMI) relative to controls (Reed & Burdett, 2002). In controls, the FGMI was larger when viewed peripherally compared to centrally and could be explained by an increased extent of receptive field size. The FGMI can be elicited with dichoptic presentation but is limited to presentation within the same hemisphere, suggesting striate or early extra-striate involvement (Biederman-Thorson, Thorson & Lange, 1971).

Stereoacuity is a relative disparity (fine stereopsis) threshold measure that differs from absolute disparity (coarse stereopsis). The former is based on discrimination of small differences in relative depth between two objects and the latter is dependent on the convergent/divergent position of the two eyes. Despite their differences, the two types of disparity might be related entities. One theory is for coarse-to-fine scale interactions in the perception of depth in which absolute disparity information feeds into a relative disparity mechanism (Marr & Poggio, 1979). More recent evidence has suggested that

fine and coarse disparity may be processed by two distinct mechanisms of stereopsis, a first-order linear mechanism and a second-order non-linear mechanism, respectively (Wilcox & Hess, 1995).

Dmax for stereopsis and motion have been shown to have similar spatial limits at all dot densities using random dot stimuli (Glennerster, 1998). Although we did not assess coarse stereopsis, children showing poor stereacuity and higher Dmax for motion may also have greater capabilities for processing absolute disparities (e.g. higher Dmax for stereopsis). In other words, the children lacking fine stereopsis may show a greater range for coarse stereopsis relative to those with fine stereoacuity. In support of this, stereodeficient individuals have been found to have a sparing of coarser scaled (non-linear or second order) stereopsis. The ability to discriminate large disparities was possible despite impairment in ability to discriminate small disparities (McColl, Ziegler & Hess, 2000). Dmax for stereopsis may involve non-linear mechanisms which are not dependent on the linear (first order) (Wilcox & Hess, 1995) and/or spatial-frequency-tuned (Schor & Wood, 1983) mechanisms required for stereoacuity.

Studies of macaque neurophysiology (Uka & DeAngelis, 2006) and functional magnetic resonance imaging in humans (Neri, Bridge & Heeger, 2004) using random dot stimuli have implicated the dorsal stream, specifically MT/hMT+ as part of the neural substrate underlying absolute but not relative disparity processing. Individuals with no measurable stereoacuity might have significant deficits within the ventral stream of visual processing but have a relative sparing within the dorsal stream (as suggested by the higher Dmax thresholds).

During occlusion therapy, as visual acuity improves, there is a shift towards more high spatial-frequency-tuned receptive fields. These high spatial-frequency-tuned receptors provide input to the ventral stream (e.g. for fine stereopsis and visual acuity) and to the dorsal stream (e.g. for coarse stereopsis and motion). At the low level, activity of high-spatial-frequency tuned receptors would increase masking of the motion signal carried by low-spatial-frequency tuned receptors reducing Dmax thresholds overall (Chang & Julesz, 1983). There could be a simultaneous decrease in the minimum relative disparity thresholds required for better stereoacuity which is based on a finer scale. On

the other hand, amblyopic children who have receptors tuned towards a coarser scale might demonstrate an increase in Dmax for motion due to a reduced masking effect and have poor stereoacuity because of an inability to detect fine degrees of relative disparity.

While these explanations could adequately explain the relationship between Dmax and stereoacuity for low-level visual processing, it does not explain the more robust correlation observed for high-pass filtered stimuli that rely on high-level, feature-matching mechanisms. High-level motion processing relies on feature matching mechanisms so fewer false-matches should give higher Dmax values. Amblyopic children with poor stereoacuity appear to have more efficient correspondence mechanisms for tracking moving features and possibly for disparity detection given that Dmax for motion and stereopsis are similar in value (Glennerster, 1998). Because absolute disparity is related to ocular vergence, the strabismic children may have a need for a greater range of coarse stereopsis due to their histories of ocular misalignment. Wilcox & Hess (1995) suggested that the presence of coarser-scaled, non-linear stereopsis may be of benefit to correspondence mechanisms by, perhaps, reducing the probability of false-matches and improving detection of object features; as well as to minimize diplopia.

Numerous fMRI studies (Lerner et al., 2003, 2006; Muckli et al., 2006) have shown reduced activation at higher areas of the ventral stream in amblyopic individuals. There is increasing evidence that higher-level areas of the dorsal stream including posterior parietal cortex (PPC) are impaired in amblyopia. Psychophysical deficits have been reported on numerous static tasks including underestimation in visual object enumeration (Sharma, Levi & Klein, 2000), and a prolonged attentional blink (Asper, Crewther & Crewther, 2003). Both of these have been reported to involve the PPC (Sathian et al., 1999 (enumeration); Marios, Chun & Gore, 2000 (attentional blink)). Attentive motion tracking, which has been shown with fMRI to involve the PPC (Culham et al., 1998), has also been reported to be defective in amblyopic children (Ho et al., 2006).

Although amblyopic children demonstrate deficiencies in both low-level and high-level motion mechanisms compared to control children, there may be a relative sparing of the high-level mechanism when fine stereopsis is absent. McKee and colleagues (McKee et al., 2003) found that the presence or absence of binocularity, regardless of etiology (deprivation, anisometropia, or strabismus), can be an indicator of psychophysical performance. In theory, it may not be entirely appropriate to use classifications of "binocular" and "non-binocular" to describe those with and without stereoacuity. For example, children with poor stereoacuity may still demonstrate some level of binocular fusion and/or coarse stereopsis at some test distance. Truly non-binocular children would demonstrate monocular suppression of visual input at all distances eliminating all cues for detection of relative and absolute disparity.

Our results provide additional support that extent of binocularity in amblyopia may be a better predictor of psychophysical performance than the etiology of the amblyogenic factor. The degree to which fine stereopsis is present (or absent) may predict performance on high-level motion tasks that are reliant on feature-matching mechanisms. The relationship between correspondence mechanisms for fine stereopsis, coarse stereopsis, and high-level motion perception warrants further study.

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# CHAPTER 4: LOW- AND HIGH-LEVEL FIRST-ORDER RANDOM-DOT KINEMATOGRAMS: EVIDENCE FROM FUNCTIONAL MAGNETIC RESONANCE IMAGING[1]

## 4.1 INTRODUCTION

The human visual system comprises at least two parallel neural pathways that are involved in form perception and motion perception. The parvocellular (P) and the magnocellular (M) pathways are responsible for aspects of form and motion processing, respectively. The two pathways remain distinct from one another as they project from the retina to the lateral geniculate nucleus (reviewed in Shapley, 1990) and to the primary visual cortex (V1). From here they continue to diverge into the extra-striate cortex although there is extensive cross-talk between the M- and P- pathways (Braddick et al., 2000). The P pathway projects ventrally to the temporal cortex (Ungerleider & Mishkin, 1982; Milner & Goodale, 1995). The M pathway in the human visual system projects dorsally and includes motion-sensitive extrastriate areas: V3A (Tootell et al., 1997), V5/MT+ (Zeki et al., 1991; Tootell et al., 1995) and regions of the posterior parietal cortex (PPC) (Cheng, Fujita, Kanno, Miura & Tanaka, 1995; Dupont, Orban, De Bruyn, Verbruggen & Mortelmans,1994; Orban et al., 2006; Sunaert, Van Hecke, Marchal & Orban, 1999). Computer-generated random dot kinematograms (RDKs) can be used to study these motion-selective brain regions.

Apparent motion with RDKs can be created by displacing a display of randomly presented dots by a certain amount in a given direction. If the displacement is small and all dots are shifted in the same direction (100% coherence), the motion perceived is smooth and continuous. As the displacement approaches the maximum displacement value (Dmax), direction discrimination of the apparent motion is still possible however the motion appears to be less coherent. As the displacement exceeds Dmax, motion direction is not reliably determined because the perceived motion appears to be incoherent, even though the dots are still moving with 100% coherence.

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Braddick (1974) classified motion perception as involving short-range (used for complex patterns, smaller displacements, briefer temporal intervals) and long-range (used for simpler patterns, larger displacements, longer temporal intervals) processes. He proposed that Dmax occurred at a displacement of approximately 15 min and represented the upper limit of the short-range mechanism. More recent research has suggested that Dmax is not a fixed value but is highly dependent on the stimulus parameters chosen and may exceed 15 min. Dmax increases with an increase in retinal eccentricity or stimulus size (Baker & Braddick, 1982; Braddick, 1974; Chang & Julesz, 1983a; Nakayama & Silverman, 1984; Todd & Norman, 1995), increase in dot size beyond 15 min (Cavanagh, Boeglin & Favreau, 1985; Morgan, 1992; Sato, 1990), decrease in dot probability (Boulton & Baker, 1993; Eagle & Rogers, 1996, 1997; Ramachandran & Anstis, 1983), and/or increase in the number of frames in the RDK (Nakayama & Silverman, 1984; Nishida & Sato; 1992; Snowden & Braddick, 1989a, b; Todd & Norman, 1995). Furthermore, Dmax increases with low or band pass spatial frequency filtering that eliminates high spatial frequencies from the stimulus (Chang & Julesz, 1983b; Cleary & Braddick, 1990; De Bruyn & Orban, 1989).

The motion system involves motion detectors that are band-pass in both spatial frequency and orientation (Anderson & Burr, 1989; Baker & Cynader, 1986; Keck, Montague & Burke, 1980; Watson & Turano, 1995). Dmax could be a psychophysical correlate for the spatial extent of the involved motion detectors. It may be proportional to the lowest spatial frequency present in a RDK which would involve the largest motion detectors (Bischoff & Di Lollo, 1990). A larger Dmax value would correspond to larger receptive field sizes. Because larger dot sizes have lower spatial frequency content they involve larger motion detectors which would be associated with a larger Dmax value. Spatial-frequency-dependent Reichardt-type motion detectors provide one possible explanation for the observed increase in Dmax with increased dot sizes but is not adequate to explain the Dmax increase observed when dot size is kept constant and dot probability is reduced. It may not even provide a complete explanation for the observed increase with larger dot sizes either. For example, Dmax still increases with increased dot size when stimuli are high-pass filtered (Eagle & Rogers, 1996; Morgan, Perry & Fahle, 1997; Smith & Ledgeway, 2001). By eliminating low spatial frequencies in the stimulus, high-pass filtering should significantly reduce the motion signal from

larger spatial-frequency-dependent motion detectors. High spatial frequency information appears to be capable of carrying motion signals most likely through feature matching of contours (Bex & Dakin, 2003; Eagle, 1998; Glennerster, 1998). If this were the case, then a larger Dmax may correlate to fewer false matches.

Feature-matching is a characteristic of the long-range (but not the short-range) motion system proposed by Braddick (1974). However, the "short-range process" has more recently been reported to involve both spatial-frequency-dependent and feature-matching motion mechanisms (Snowden & Braddick, 1990). Since Braddick's short-range and long-range classification, several other theories of motion perception have evolved. For example, Cavanagh and Mather (1990) suggest that low-level mechanisms process first-order stimuli (luminance- or color- defined) and that high-level mechanisms process second-order motion stimuli (motion- and stereo-defined). Lu and Sperling (reviewed in 2001) propose three separate motion systems: a first-order system responding to luminance-defined stimuli, a second-order system responding to contrast- or motion- defined stimuli, and a third-order system which is based on the "salience map" of a moving stimulus.

Nishida and Sato (1995) propose a model in which low-level and high-level mechanisms are based on spatial-frequency-tuned motion detectors and feature matching mechanisms, respectively (reviewed in Sato, 1998). Sato (1988) suggests that the high-level process is not limited to second-order stimuli only but can be active for first-order stimuli if certain stimulus conditions are met (i.e. low dot densities and/or large dot sizes). He proposes that the larger Dmax obtained using first-order RDK stimuli with reduced dot density and increased dot size can be explained by high-level motion mechanisms that are preceded by a low-level feature extraction stage. As dot probability is decreased and dot size is increased, there is a switch from low-level processing towards high-level processing for Dmax. In support of this, Smith and Ledgeway (2001) also suggest that low- and high-level mechanisms operate simultaneously rather than separately. With any given motion stimulus, the most efficient mechanism predominates and this is dependent on stimulus parameters. Throughout this study, we refer to spatial-frequency-dependent mechanisms as low-

level and to feature-matching mechanisms as high-level (Nishida and Sato, 1995; Sato, 1998).

Feature-matching mechanisms provide a feasible explanation for the increase in Dmax observed with both the increased dot size and decreased dot probability conditions (Eagle and Rogers, 1996). Altering stimulus parameters in both cases reduces the overall dot density in the stimulus. In other words, reducing dot probability and increasing dot size both decrease the number of dots in a display of a fixed size. Dmax appears to increase when the complexity of a stimulus is reduced presumably due to greater efficiency of feature-matching mechanisms (Sato, 1998). A stimulus onset asynchrony (SOA) effect such that Dmax increases with increasing SOA is also suggestive of high-level feature-matching mechanisms since low-level mechanisms do not follow Korte's third law which states that Dmax increases as SOA increases (reviewed in Sato, 1998). There are numerous reports of an SOA effect both with increased dot size (Cavanagh et al., 1985; Sato, 1998) and with reduced dot density (Ramachandran & Anstis, 1983; Sato, 1998).

While there is indirect behavioural data suggesting that Dmax for less complex, luminance-defined RDKs involves higher motion processing mechanisms than Dmax for more complex RDKS, there has been no direct evidence showing this to be true in humans. To investigate the extent of high-level involvement in the perception of first-order RDKs, we used functional magnetic resonance imaging. We used three RDK stimuli: a small, dense dot baseline condition, a reduced dot probability condition and an increased dot size condition. Dot sizes were selected to fall in a range above 20 min because smaller dot sizes have been shown to have little effect on Dmax (Cavanagh et al., 1985; Morgan, 1992; Sato, 1990). The same RDK parameters have been used in two of our previous studies both of which confirm the baseline condition to be biased towards low-level mechanisms and the reduced dot probability and increased dot size conditions towards high-level motion mechanisms as intended (Ho & Giaschi, 2006, 2007). Our hypothesis was that there would be greater involvement of high-level areas of the dorsal pathway for the latter two high-level RDK conditions relative to the baseline condition. The results showed increased activation in extrastriate motion areas (putative V3A, MT+, PPC) in addition to a very robust decrease in cortical activity within

the posterior occipital cortex when activation for high-level RDKs is compared to that for the baseline low-level RDK.

## 4.2 PARTICIPANTS

Four subjects were tested ranging in age from 14 to 29 years (*M* = 19.9 yrs, *SD* = 7.5 yrs). All of the subjects were visually mature as Dmax has been shown to reach adult levels between age 7 to 8 years (Parrish, Giaschi, Boden & Dougherty, 2005). Each subject had distance and near monocular line visual acuity (VA) equivalent to or better than, respectively, 6/6 or 0.4 M (Jose & Atcherson, 1977). Stereoacuity, assessed using the Randot Stereotest (Stereo Optical Co., Inc.), was required to be equivalent to or better than 40 sec of arc. No subject had a history of ocular pathology or abnormal visual development.

## 4.3 PSYCHOPHYSICS

Prior to the fMRI sessions, individual Dmax thresholds for direction discrimination were determined in the psychophysics laboratory. This was done to equate the difficulty level of the behavioural task in the scanner across subjects. Also, we were interested in looking at cortical activation for RDKs displaced at Dmax and this threshold value varies amongst subjects.

### 4.3.1 Stimulus

The psychophysical tasks were programmed in Matlab and run on a Macintosh Power G4 laptop computer. The stimuli were displayed on a 17" monitor with a resolution of 800 x 600 (horizontal x vertical) pixels and a refresh rate of 60Hz. Subject responses were collected with a Gravis Gamepad Pro.

The visual stimuli for all conditions of the Dmax task consisted of randomly generated patterns of white dots (100 cd/$m^2$) on a black background (5 cd/$m^2$). The viewing distance was 70 cm. The entire random-dot display subtended a visual angle of 25.4 x 19.2 deg (horizontal x vertical).

Each subject performed the task under three display parameters in each eye: 20 min dot size at 5% dot density (Condition 1), 20 min dot size at 0.5% dot density (Condition 2), and 1 deg dot size at 5% dot density (Condition 3). The dot sizes listed above represent the diameter of each round dot in the display. Each RDK consisted of 10 frames and the duration of each frame presentation was 200ms (12 screen refreshes at 60Hz). No inter-stimulus interval was used. A total of six threshold values were recorded for each subject.

### 4.3.2 Procedure

The study was approved by the University of British Columbia's Behavioural Research Ethics Board. All thresholds were determined in one session that lasted approximately 30 minutes. For the fMRI phase of the study, the eyes were dissociated by using red-green filters to allow for monocular testing (see 4.4.1). To be consistent, the psychophysical thresholds were determined while the subjects wore the same MRI-compatible glasses with the red-green filters in place such that the right eye viewed through a red filter and the left eye through a green filter. A neutral density filter was used to make the right and left images equiluminant. Prescribed optical correction was worn under red-green filters throughout testing for subjects requiring refractive correction. The non-tested eye was occluded. Testing was performed under diffuse illumination with lights directed away from the display screen to prevent glare. Subject responses were self-paced and subjects were asked to guess the correct response if they were unsure. Feedback was provided for the subjects throughout the trials. The eye tested first was randomly varied for each subject.

For each trial, the random dot display was displaced by a given jump size, upward or downward, at 100% coherence, for 10 consecutive frames of animation. The task was direction discrimination of the apparent motion. A two-alternative forced-choice (2AFC) paradigm was used, in which the probability of accurately guessing the correct response was 50%.

As the displacement increased, the task of direction discrimination became more difficult. All conditions began with a jump size of 0.3 deg that all participants could perform easily with 100% accuracy. Jump size was adjusted such that it increased after

two correct responses, and decreased after one incorrect response. Jump size was halved, beginning at the 4th reversal, for each incorrect response. The staircase ended after the 15th reversal in jump size or after 60 trial presentations, whichever occurred first. Throughout testing, subjects were asked to maintain fixation on a cross in the middle of the screen. The levels were chosen based on previous findings (Ho & Giaschi, 2006; 2007). To ensure that the task was understood before each session, the participants were asked to do a practice trial.

### 4.3.3 Threshold Calculations

Psychometric functions were fitted using the Psignifit toolbox version 2.5.41 for Matlab (see http://bootstrap-software.org/psignifit/) which implements the maximum-likelihood method described by Wichmann and Hill (2001). Threshold was defined using the stimulus level at which performance was 75% correct, halfway between the guess rate (50% correct) and perfect performance (100% correct) for a 2AFC paradigm. The six thresholds were recorded to be used later in the fMRI scans below.

The psychophysical thresholds are depicted in Figure 4.1. As expected, Condition 2 and 3 (the high-level conditions) gave larger Dmax values than Condition 1 (the baseline low-level condition).

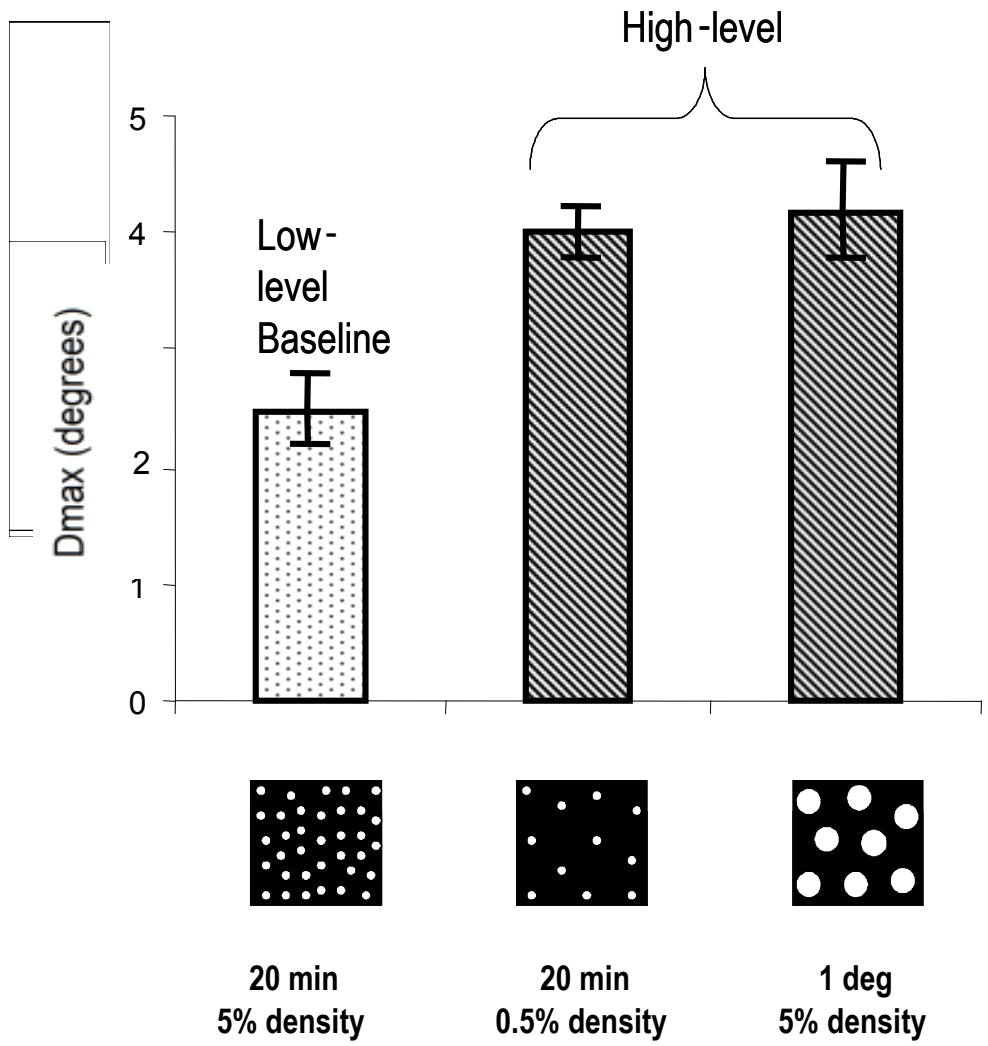


**Figure 4.1:**

Mean Dmax threshold values obtained for the 3 RDK conditions used. The threshold values represent the dot displacement at which 75% accuracy was obtained in the direction discrimination task. The mean thresholds averaged across both eyes is shown (thresholds did not significantly differ between eyes). Error bars represent standard errors.

## 4.4 FUNCTIONAL MRI

### 4.4.1 Data Acquisition

Each participant completed a scanning session that lasted approximately one hour. During a session, echo-planar imaging (EPI) was used to collect functional data in four T2*-weighted scans (TE = 30 ms, TR = 2000 ms). The field of view (FOV) was 240 mm; 3 mm isotropic voxels were acquired using an 80 x 80 mm matrix. The images were reconstructed with a 128 x 128 mm matrix which resulted in an effective voxel size of 1.88 x 1.88 x 3 mm. Volumes were collected in 36 interleaved axial slices (slice thickness: 3 mm, inter-slice gap: 1 mm).

At the end of the scanning session a high-resolution anatomic brain image was collected. Transverse slices were acquired with a T1-weighted scan that was 6 minutes and 34 seconds in duration (FOV: 256 mm, matrix: 256 x 256, voxel size: 1 x 1 x 1 mm).

The visual stimuli were viewed by participants while lying in a Philips Gyroscan Intera 3 Tesla MRI scanner with a phased array head coil (SENSE). The stimuli were back projected with an LCD projector (resolution: 800 x 600; refresh rate: 60 Hz) onto a screen that was 53 cm behind the participant's head and viewed through a mirror that was 15 cm from the participant's eyes. Subject responses were obtained using a fiber optic response system (Lumitouch).

Participants practiced all of the tasks prior to entering the scanner. Red and green filters were placed in a MRI compatible frame with the red filter always in front of the right eye. The red-green glasses were worn throughout the entire scan. Red and green filters, cut from the same filter sheets, were placed over the projector, and changed throughout the scan, to allow for monocular testing. With the red filter in place, the stimulus was visible to only the right eye. With the green filter in place, the stimulus was visible to only the left eye. Without filtering the stimulus, it was visible to both eyes. The luminance of the red and green light from the filtered projector was balanced by placing a 0.3ND filter over the red filters both on the projector and in the frame. The eye tested first was randomly varied by changing the order in which the red and green filters were placed over the projector.

### 4.4.2 Visual Stimuli & Experimental Design

The RDKs used for the psychophyiscs were modified into two different block design fMRI stimuli that were run on each eye. The stimuli were composed of white dots on a black background with a central white fixation cross (display width: 25.3 deg; height: 19.4 deg). The dots moved either upwards or downwards with 100% coherence. Figure 4.2 illustrates the fMRI paradigm used in each of the runs.

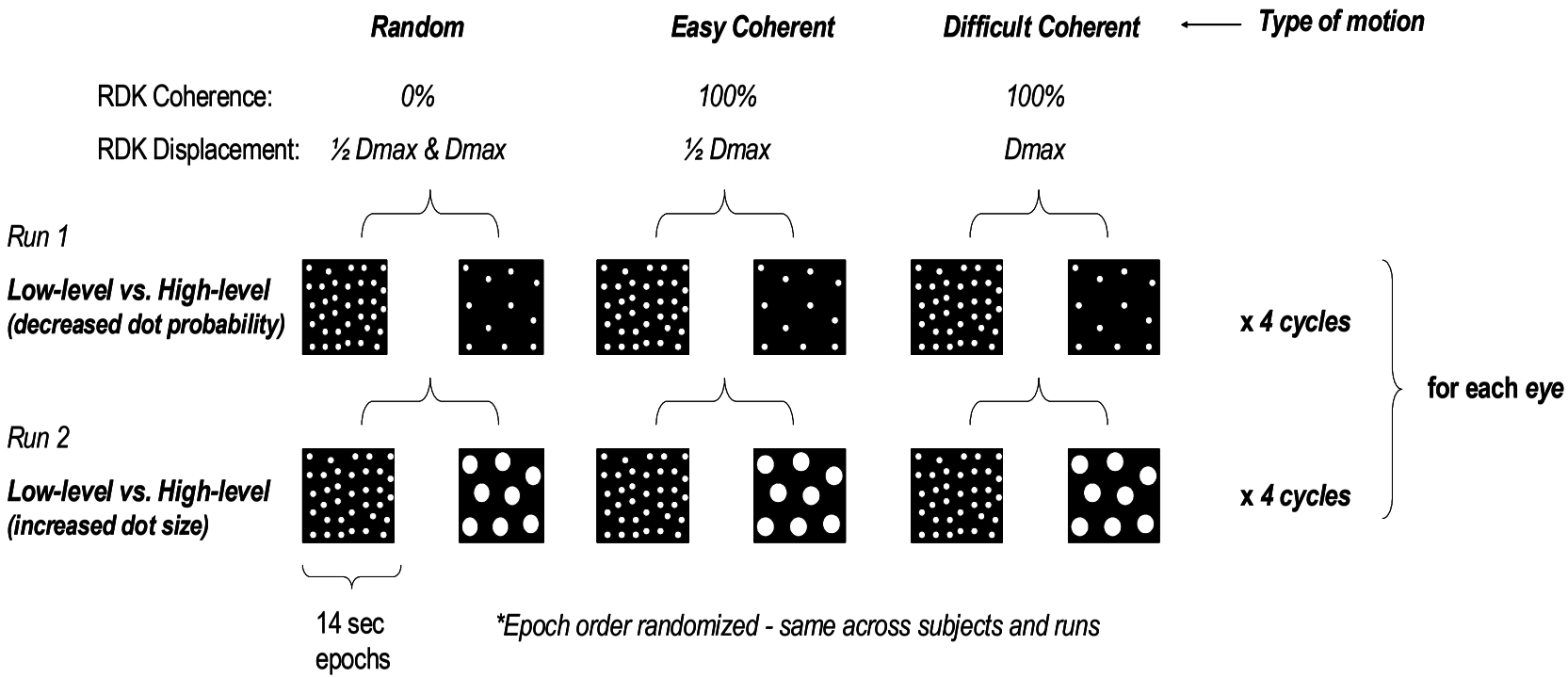


**Figure 4.2:**

Paradigm used for functional MRI scans. Each of the two Dmax runs had six epochs that were repeated for four cycles. The first run and the second run differed only in the high-level RDK stimulus used (reduced dot density or increased dot size). Both runs were based on the same block design and the order of the epochs was presented in the same predetermined, randomized order for each run and for every subject.

Each of the two Dmax runs had six epochs that were repeated for four cycles. Each epoch was 14 s giving a total run time of 336 s. The psychophysical Dmax thresholds for both eyes of each participant were used to determine the jump sizes in each epoch. A total of 6 thresholds were needed per subject (3 display conditions x 2 eyes). The epochs were designed to compare cortical activation for: 1) random motion; coherent motion with relatively easy (dot displacement at ½ Dmax); and more difficult (dot displacement at Dmax) direction discrimination; and 2) the baseline low-level RDK (Condition 1); and the two high-level RDK conditions (Condtions 2 or 3).

The six epoch parameters [dot display; dot displacement; motion coherence] for the first Dmax run are listed below:
1) 20 min dots at 5% density (Condition 1); Dmax; 100%
2) 20 min dots at 5% density (Condition 1); ½ Dmax; 100%
3) 20 min dots at 5% density (Condition 1); Dmax or ½ Dmax (randomized); 0%
4) 20 min dots at 0.5% density (Condition 2); Dmax; 100%
5) 20 min dots at 0.5% density (Condition 2); ½ Dmax; 100%
6) 20 min dots at 0.5% density (Condition 2); Dmax or ½ Dmax (randomized); 0%

The six epoch parameters for the second Dmax run were the same as above for epochs 1-3 but with the following changes for epochs 4-6:
4) 1 deg dots at 5% density (Condition 3); Dmax; 100%
5) 1 deg dots at 5% density (Condition 3); ½ Dmax; 100%
6) 1 deg dots at 5% density (Condition 3); Dmax or ½ Dmax (randomized); 0%

Both runs were based on the same block design. The order of the epochs was presented in the same predetermined randomized order for each run and for every subject. For the 4 cycles, the order of the 6 epochs was: 1$^{st}$ cycle [6,1,5,4,2,3], 2$^{nd}$ cycle [5,1,3,2,4,6], 3rd cycle [6,4,2,3,1,5], 4$^{th}$ cycle [3,2,4,5,1,6]. The order of blocks was symmetrical (cycles 3 and 4 were the reverse of the order for cycles 1 and 2) to reduce the influence of linear trends. Every epoch contained 5 trials. Each trial was composed of 10 frames (the same number as in the psychophysical tasks) followed by an inter-trial interval of 80 msec during which a direction discrimination response was made. Participants had the task on all trials of pressing one of two buttons to indicate the

perceived direction of the apparent motion (up or down) for each trial (even for the random motion trials in which neither was correct). Accuracy of behavioural responses was recorded for each of the coherent motion trials (Dmax, ½ Dmax) to confirm that level of difficulty and attention to the task were similar across subjects.

### 4.4.3. Data Analysis & Results

Data preprocessing and statistical analysis were conducted with BrainVoyager QX (Brain Innovation). Prior to analysis, inter-slice time differences were removed from the data with an algorithm involving linear interpolation over time. All volumes were then corrected for small translational and rotational head movements by aligning to the first volume of each run using a nine-parameter rigid-body intensity-based algorithm with tri-linear interpolation across eight neighboring voxels. Temporal high-pass filtering (3 cycles in time course) and a linear trend removal algorithm were used to eliminate temporal drifts from the data (e.g. physiological and scanner noise). The functional volumes were co-registered with the anatomic image. The data were then spatially normalized to stereotaxic space (Talairach & Tournoux, 1988) and superimposed on an averaged anatomic volume made from all subjects, to establish spatial correspondence between brain areas.

#### *4.4.3.1 Delineating the motion-selective regions-of-interest*

To determine the low-level and high-level motion-sensitive areas of interest, the general linear model (GLM) was used for statistical analysis. Data from the Dmax runs were analyzed with a fixed-effects whole brain 3 x 2-factor ANOVA to identify low- and high-level regions-of-interest (ROIs). A boxcar function, convolved with the BrainVoyager default haemodynamic response function (double-gamma function model; Friston et al., 1998) was used to model the data and maps of the *t* statistic were created, with a Bonferroni correction for multiple comparisons ($p<.001$). The ANOVA was of the following factorial design:

***Factor A*** *(3 levels): Type of Motion [Random, Easy coherent, Difficult coherent]*
***Factor B*** *(2 levels): Type of RDK [Low-level, High-level]*

The first main effect tested looked at activation differences for direction discrimination of coherent motion at ½ Dmax (easier task; Factor A2), coherent motion at Dmax (more difficult task; Factor A3) displacements relative to random motion (0% coherence) at random displacements (Factor A1). The second main effect, and that pertaining specifically to the test of our hypothesis, looked at activation differences between experimental (high-level; Conditions 2 or 3) versus the baseline (low-level; Condition 1) RDKs. For the ANOVA, the first predictor for each factor (Factor A: random motion; Factor B: low-level Condition 1) was excluded and used as the implicit baseline. Factor A x Factor B interactions were also tested.

There was no main effect of type of motion (Factor A: coherent (easy or hard) motion vs. random motion) but there was a robust main effect of type of RDK (Factor B: high-level vs. low-level). There were no significant interactions.

The brain areas showing significant cortical activation for the main effect of type of RDK are listed in Table 4.1. Only brain regions showing significant activation for all high-level RDKs are listed. Overall, activation was limited to the posterior brain regions only. The BrainVoyager ROI analysis tool was used to demarcate the regions-of-interest (ROIs) listed. No cluster size limit or smoothing algorithm was applied to define the areas. The occipital ROI was considerably large given that the stimulus activated most of the lower visual areas in both hemispheres. The MT+ ROI was the cluster of contiguous activated voxels in the region of the parietal-temporal-occipital junction in each hemisphere. The stereotaxic locations of putative area V3A (e.g. Dupont et al., 1994; Sunaert et al.,1999; Tootell et al., 1997) and MT+ (e.g. Sunaert et al., 1999; Tootell et al., 1995; Zeki et al., 1991) were consistent with locations reported in previous studies. Most parietal cortex activation was localized to the posterior-dorsal regions of the intraparietal sulcus (IPS) (Dupont et al., 1994; Orban et al., 2006; Sunaert et al., 1999).

**Table 4.1:** Regions-of-interest defined by significant cortical activation differences for high-level vs. baseline low-level RDK comparisons (significance level of p<0.001 Bonferroni-corrected)

| ***High-level RDKs > Low-level RDK*** | **ROI** | | **Hemisphere** | **Extent ($mm^3$)** | **X** | **Y** | **Z** | **Average t-statistic** | **Threshold significance** |
|---|---|---|---|---|---|---|---|---|---|
| | Occipital | | R/L | 39621 | 1 | -84 | -13 | -10.48 | $p<10^{-10}$ |
| | Putative V3A | | R | 151 | 26 | -78 | 16 | 6.30 | $p<10^{-9}$ |
| | Parietal | *POIPS* | R | 210 | 11 | -79 | 35 | 6.46 | $p<10^{-9}$ |
| | | | L | 113 | -19 | -72 | 42 | 6.09 | $p<10^{-9}$ |
| | | *VIPS* | R | 78 | 17 | -87 | 29 | 5.96 | $p<10^{-9}$ |
| | | *DIPSM* | R | 227 | 18 | -69 | 50 | 6.57 | $p<10^{-9}$ |
| | MT+ | | R | 67 | 44 | -68 | -2 | 5.98 | $p<10^{-9}$ |

Talairach coordinate system for stereotaxic location: X: right-left Y: anterior-posterior Z: dorsal-ventral
POIPS: parieto-occipital intraparietal sulcus; VIPS: ventral intraparietal sulcus; DIPSM: dorsal intraparietal sulcus medial

The *t* statistic values listed in Table 4.1 show that there is a significant decrease in cortical activation in occipital areas and a significant increase in cortical activation in putative area V3A, MT+ as well as PPC when the activation for high-level stimuli was compared to that for the low-level stimulus. The relative decrease in activation in posterior occipital cortex is a robust finding but activation in high-level areas appears to be more variable. Furthermore, although monocular viewing should stimulate both hemispheres equally in each eye, a right hemisphere bias was noted in the high-level activation regardless of which eye was viewing.

Figure 4.3 shows the general pattern of cortical activation observed in a sample of axial, coronal, and sagittal slices for the high-level vs. low-level comparison. Overall, there was a relative decrease in cortical activation in posterior occipital regions and a relative increase in activation in extrastriate motion areas (putative V3A, MT+, and PPC). The statistical maps are shown on the group-averaged anatomic image.

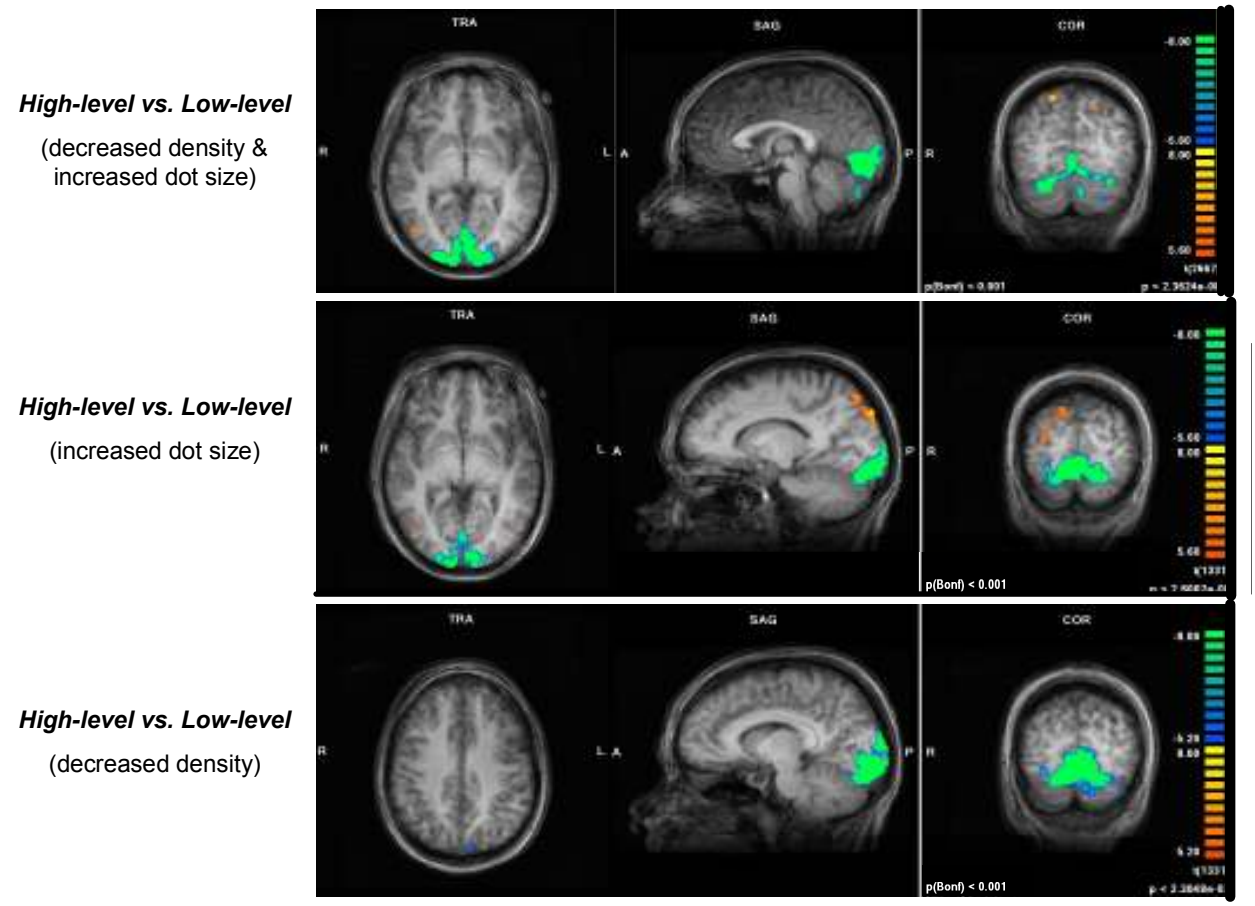


**Figure 4.3:**

Sample slices of fMRI images showing the regions-of-interest used in the ROI analysis (at a significance level of $p<0.001$ with a Bonferroni correction for multiple comparisons). Blue-green colors represent significant negative *t*-statistic values (decreased activation relative to baseline) and red-yellow colors represent significant positive *t*-statistic values (increased activation). ***Top row images***: axial, sagittal and coronal slices showing area MT+, occipital cortex, and PPC activation, respectively. ***Middle row images***: axial slice showing MT+ activation; sagittal and coronal slices show activation in putative area V3A which is inferior and posterior to activation in PPC. ***Bottom row images***: axial, sagittal and coronal slices showing primarily decreased activation in posterior occipital cortex.

#### *4.4.3.2 Post-hoc region-of-interest analyses*

In order to obtain percent signal change information, a series of group post-hoc contrasts were tested within the four specific ROIs delineated above (all data included): occipital, putative V3A, MT+, and parietal areas. For the post-hoc analysis, the parietal ROI grouped together all active parietal voxels listed in Table 4.1.

Because ROI analyses involve a smaller number of comparisons than whole brain analyses, *t* scores were significant at $p < .05$, uncorrected. The contrasts tested compared activation for: 1) easy coherent motion vs. random motion; 2) difficult coherent motion vs. random motion; 3) difficult coherent motion vs. easy coherent motion; and 4) high-level RDKs vs. low-level RDK. The only comparisons meeting statistical significance were the contrasts tested for high-level RDKs vs. low-level RDK as expected. This was observed for all four ROIs. Figure 4.4 illustrates the percent signal change within each of the four motion-sensitive areas for these contrasts. Putative area V3A, MT+ and parietal ROIs show a significant increase in activation (all $p$=0.00) whereas the occipital ROI showed a significant decrease in activation for the comparison of high-level vs. low-level ($p$=0.00). In addition to being consistent between ROIs, this statistical finding was also very consistent across subjects. The individual and group percent signal change results are given in Table 4.2.

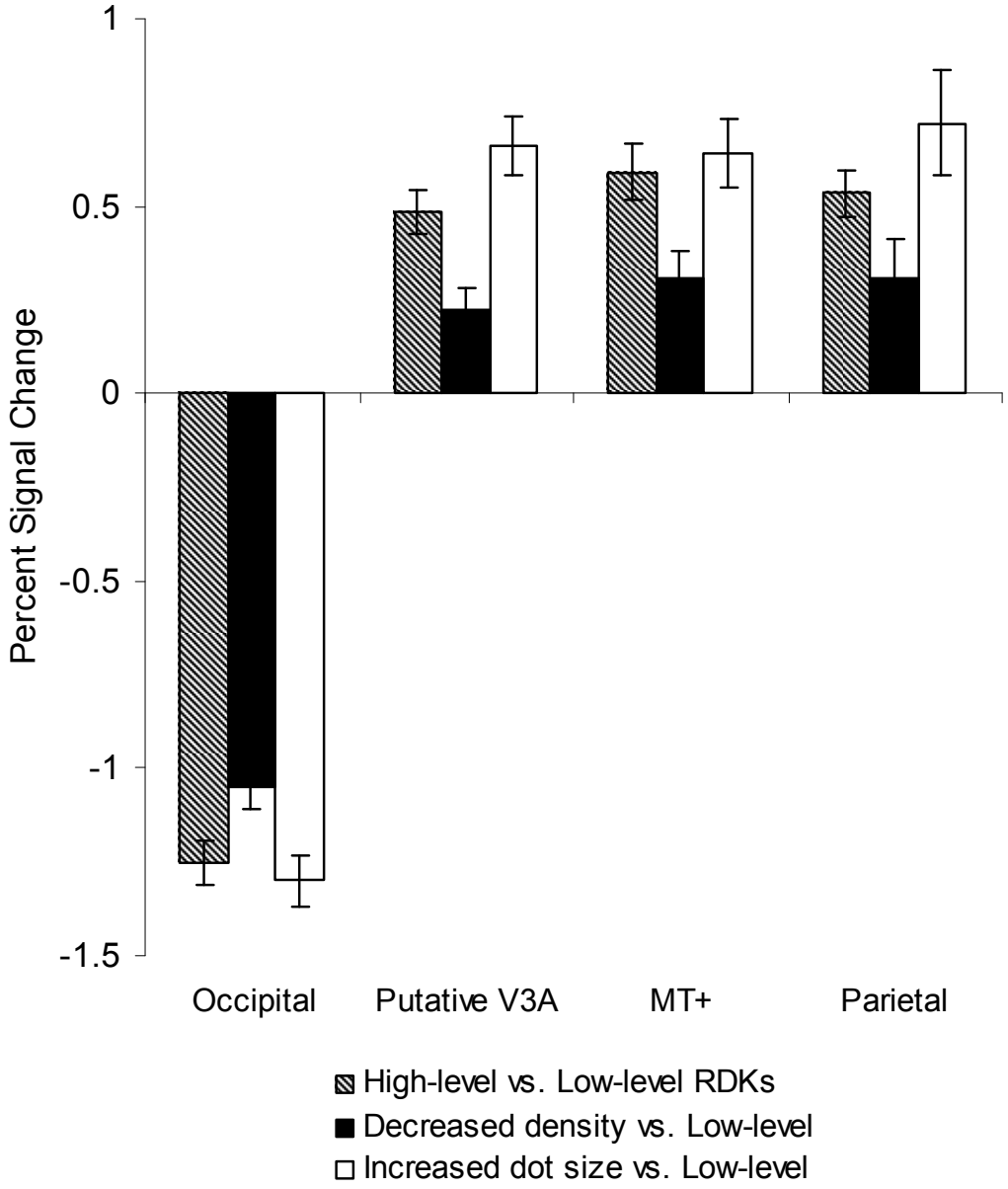


**Figure 4.4:**

Bar graph depicting cortical activation in the 4 ROIs for comparison between high-level and low-level RDK stimuli. There was a statistically significant decrease in cortical activation for high-level RDKs relative to the low-level baseline RDK in occipital cortex. In contrast, for the same comparison, there was a statistically significant increase in cortical activation in extrastriate motion areas: putative area V3A, MT+, and PPC.

**Table 4.2:** Individual subject and group percent signal change results for high-level vs. low-level RDK comparisons

| ***ROI*** | | ***Activation difference: High-level (both) vs. Low-level*** | *Percent signal change (significance)* | ***Activation difference: High-level (decreased density) vs. Low-level*** | *Percent signal change (significance)* | ***Activation difference: High-level (increased dot size) vs. Low-level*** | *Percent signal change (significance)* |
|---|---|---|---|---|---|---|---|
| **Occipital** | Subject A | * | -0.24 (p=0.00) | * | -0.29 (p=0.00) | * | -0.18 (p=0.00) |
| | Subject B | * | -0.19 (p=0.00) | * | -0.27 (p=0.00) | * | -0.14 (p=0.00) |
| | Subject C | * | -0.34 (p=0.00) | * | -0.43 (p=0.00) | * | -0.28 (p=0.00) |
| | Subject D | * | -0.15 (p=0.00) | * | -0.07 (p<0.05) | * | -0.34 (p=0.00) |
| | *Group* | * | *-1.25 (p=0.00)* | * | *-1.05 (p=0.00)* | * | *-1.30 (p=0.00)* |
| | | | | | | | |
| **Putative V3A** | Subject A | | +0.03 (p=0.10) | | +0.01 (p=0.62) | | +0.50 (p=0.10) |
| | Subject B | * | +0.10 (p<0.000005) | * | +0.08 (p<0.005) | * | +0.13 (p<0.00005) |
| | Subject C | * | +0.20 (p=0.00) | * | +0.12 (p<0.00005) | * | +0.28 (p=0.00) |
| | Subject D | | +0.02 (p=0.31) | | 0.00 (p=0.93) | | +0.08 (p=0.07) |
| | *Group* | * | *+0.48 (p=0.00)* | * | *+0.22 (p<0.0001)* | * | *+0.66 (p=0.00)* |
| | | | | | | | |
| **MT+** | Subject A | * | +0.16 (p=0.00) | * | +0.14 (p<0.0001) | * | +0.18 (p=0.00) |
| | Subject B | * | +0.07 (p<0.05) | | +0.04 (p=0.28) | * | +0.10 (p<0.01) |
| | Subject C | * | +0.10 (p<0.0005) | | +0.06 (p=0.09) | * | +0.12 (p<0.001) |
| | Subject D | * | +0.07 (p<0.05) | | +0.07 (p=0.066) | | +0.07 (p=0.14) |
| | *Group* | * | *+0.59 (p=0.00)* | * | *+0.31 (p<0.00005)* | * | *+0.64 (p=0.00)* |
| | | | | | | | |
| **Parietal** | Subject A | * | +0.08 (p<0.0005) | * | +0.15 (p<0.005) | * | +0.20 (p<0.0005) |
| | Subject B | * | +0.13 (p=0.00) | * | +0.13 (p<0.05) | * | +0.22 (p<0.00005) |
| | Subject C | * | +0.30 (p=0.00) | * | +0.20 (p<0.0005) | * | +0.39 (p=0.00) |
| | Subject D | | +0.01 (p=0.71) | | -0.16 (p=0.002) | | -0.09 (p=0.21) |
| | *Group* | * | *+0.54 (p=0.00)* | * | *+0.31 (p<0.005)* | * | *+0.72 (p=0.00)* |

*denotes significant activation differences with p<0.05

Figure 4.5 charts the average percent signal change across an epoch time course for each of the conditions tested. The conditions are grouped according to RDK type: low-level and high-level. The activation in each of the four ROIs is shown separately. In the occipital ROI, cortical activation for low-level and high-level RDKs is unquestionably in opposite directions. Cortical activation in putative area V3A, MT+, and parietal cortex shows a subtle trend towards activation in a direction opposite to that observed in the occipital ROI. In general though, there is much greater variability in cortical activation within the high-level ROIs.

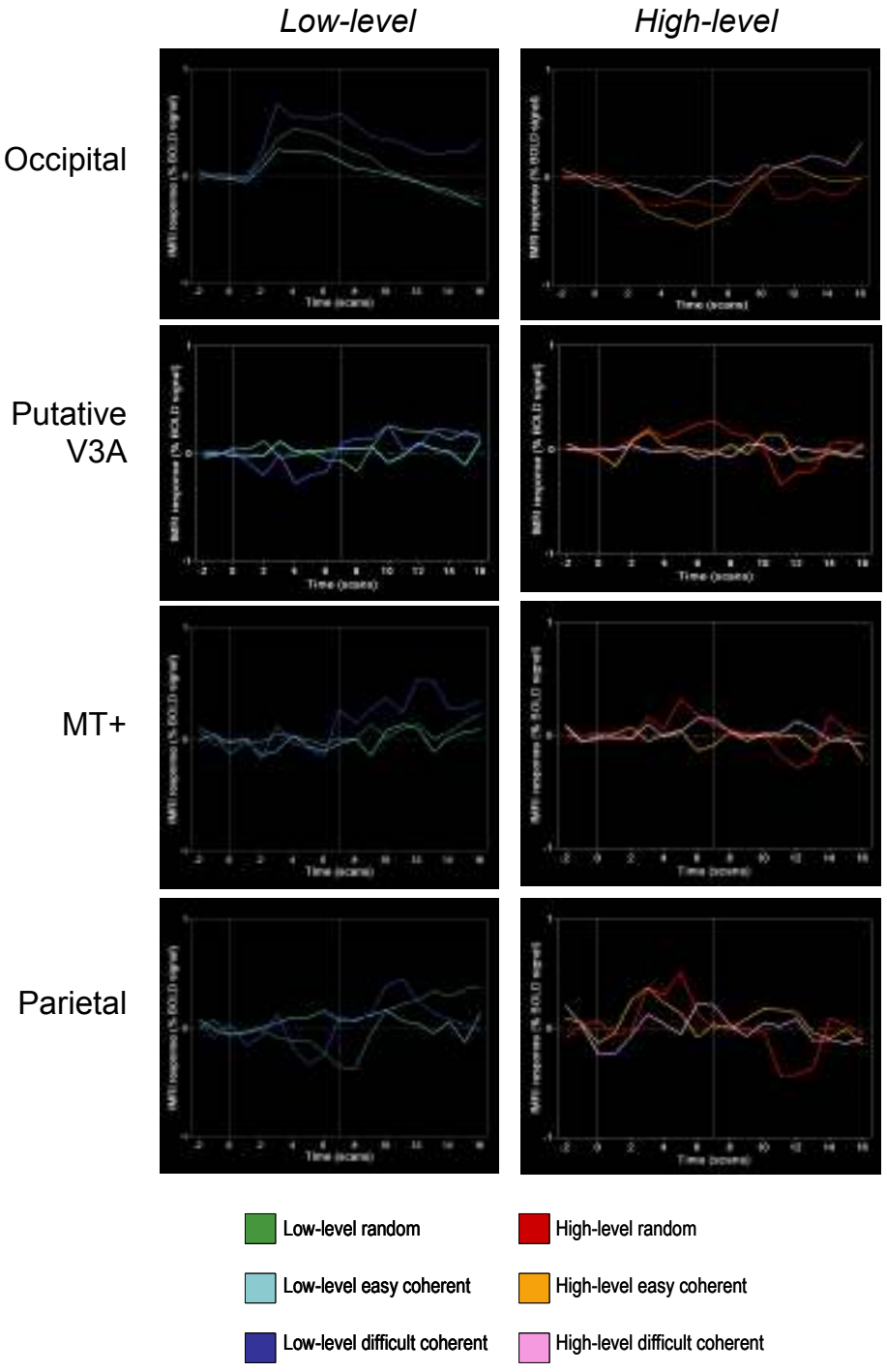


**Figure 4.5:**

Percent signal change across an epoch time course for each condition tested. Conditions are shown grouped according to RDK type: low-level and high-level. The activation in each of the four ROIs is plotted separately. In the occipital ROI, cortical activation for low-level and high-level RDKs is in opposite directions. Cortical activation in putative area V3A, MT+, and PPC show a subtle trend towards activation in a direction opposite to that observed in the occipital ROI.

## 4.5 DISCUSSION

Our findings are consistent with previous reports that an increase in Dmax is observed for RDKs with reduced dot probability (Boulton & Baker Jr., 1993; Eagle & Rogers, 1996, 1997; Ramachandran & Anstis, 1983), and increased dot size (Cavanagh et al., 1985; Morgan, 1992; Sato, 1990). It has been proposed that Dmax can be limited by the receptive field size of low spatial-frequency-tuned motion detectors and/or by the limits of spatial feature matching. This occurs at low- and high- levels of motion processing, respectively, and the mechanism that dominates is largely dependent on the stimulus parameters chosen (Nishida and Sato, 1995; Sato, 1998; Snowden & Braddick, 1990; Smith & Ledgeway, 2001). Decreasing dot density and/or increasing dot size of first-order, luminance-defined RDKs create a bias towards high-level motion mechanisms. In agreement with this, we consistently found a robust decrease in activation within posterior occipital cortex with the decreased dot density and reduced dot size RDKs relative to the low-level baseline RDK. We also found a significant increase in activation in putative area V3A, area MT+, and posterior parietal regions of the IPS with the high-level RDKs relative to low-level stimuli (especially for the increased dot size condition). As we predicted, there is less low-level (occipital) and greater high-level (extrastriate) involvement with first-order RDKs biased towards high-level mechanisms.

Physiological evidence shows posterior parietal areas in the macaque to be involved in high-level motion perception (Assad & Maunsell, 1995). Neurons in lateral intraparietal area (LIP) have been identified in the macaque monkey as an important parietal region involved in high-level direction discrimination (Williams, Elfar, Eskandar, Toth & Assad, 2003). Williams and colleagues suggest the role of parietal neurons in motion perception is to fill in gaps when visual information is incomplete or ambiguous. This could be the case in perceiving apparent motion for sparse displays such as random dot displays with low dot densities and/or large dot size (Sato, 1998), and to classical long-range stimuli (Braddick, 1974). It has been suggested that area LIP in the macaque is homologous to regions near the IPS, specifically between POIPS and DIPSM, in humans (Orban et al., 2006, Muri, Iba-Zizen, Derosier, Cabanis, Pierrot-Deseilligny, 1996; Sereno, Pitzalis & Martinez, 2001; Simon, Mangin, Cohen, Le Bihan & Dehaene,

2002). These specific parietal areas were found to be active with our high-level RDK stimuli.

The IPS regions that were involved with our high-level RDKs are consistent with those previously reported in humans using first-order stimuli. Functional MRI has shown significant parietal lobe involvement in high-level motion perception (Culham et al., 1998; Dupont et al., 1994; Sunaert et al., 1999). Culham and colleagues found that parietal regions near the IPS and, to a lesser extent, MT+ and parts of the lateral-occipital cortex near V3A are involved in multiple-object tracking. Additionally, they found activation in frontal areas of brain. Attentive tracking (Cavanagh, 1992) is a high-level motion task that involves feature-matching mechanisms. The high-level RDKs used in this study are likely mediated by feature-matching mechanisms and the processing of RDK apparent motion in this study appears to involve similar motion-sensitive regions as attentive tracking. Our activation, however, appears to be limited to posterior regions of the brain only, most likely because our task is less cognitively demanding. Claeys and colleagues (Claeys, Lindsey, De Schutter & Orban, 2003) also report on activation in similar regions of the IPS that responded specifically to luminance-based motion stimuli. However, they also discuss a second high-level system involving the inferior parietal lobe that appears to be selectively responsive to saliency-based motion stimuli.

Several studies have looked at the spatial limits of direction-selective neurons, which can be considered the neural correlate to the psychophysical measure of Dmax. Mikami and colleagues (Mikami, Newsome & Wurtz, 1986) found that the upper spatial limit of displacement (in the preferred direction) to which direction-selective neurons would respond was three times as large for MT than V1 in alert macaques. The authors concluded that V1 input does not fully account for the directional mechanisms in MT. It is likely that high-level input from extra-striate motion areas (or low-level input from other direction-selective occipital regions) can modify direction-selective responses in MT. In contrast, Churchland and colleagues (Churchland, Priebe & Lisberger, 2005) found that neurons in V1 and MT retained direction selectivity for similar displacement limits, suggesting a strong V1 influence to the direction selectivity in MT. One significant difference between the two studies was that electrophysiological recording in

the latter study was done in certain cases with anesthetized macaques. This could certainly dampen activity in higher-level visual areas and reduce feedback that might normally modulate responses in V1 and/or MT in alert macaques.

In this study, there was a robust finding of a relative decrease in activation within the posterior occipital cortex for high-level relative to low-level RDK stimuli. V1 activity in the perception of long-range apparent motion has been shown to be mediated by feedback from MT+ (Sterzer, Haynes & Rees, 2006). Thus, it is possible that increased activity in PPC or MT+ has an inhibitory effect on neural activity in lower-visual areas in occipital cortex, accounting for the decreased activation observed in this study. This may be a strategy of increasing efficiency of the high-level motion system by limiting competing inputs from the low-level motion system.

There was greater variability in the pattern of activation observed for each of the higher-level ROIs as seen in the graphs showing average activation across an epoch time course (Figure 4.5). This might be explained by fluctuations in attentional state throughout the course of the scan. The occipital activation, however, appeared to be less susceptible to variations in attentional state. Attention has been reported to modulate activity in MT+ (Beauchamp, Cox & DeYoe, 1996; O'Craven, Rosen, Kwong, Treisman & Savoy, 1997; Treue and Maunsell, 1996; Buchel et al., 1998) and the PPC (Beauchamp et al., 1996). Although tracking of behavioural responses during the fMRI runs in this study suggested that level of performance was similar amongst subjects, it is likely that level of attention may have varied throughout the time course of the scans. It is interesting, but not surprising, that in many cases, the random motion condition was associated with greater activation (although not statistically significant) relative to the easy and difficult coherent motion conditions. Because subjects were forced to discriminate the direction of motion in the absence of coherent directional cues, this task is the most challenging and demands the most attention.

Although it is not possible to definitively conclude that the right hemisphere bias that we observed in the activation of extra-striate motion areas truly exists, it is interesting to note that other studies have also found right hemispheric biases in motion processing. In a study of attentional processes in parietal cortex using a stimulus of colored moving

dots, Shulman and colleagues found a right hemisphere bias towards motion selectivity in high-level motion areas (Shulman, Avossa, Tansy & Corbetta, 2002). This was noted specifically during the test period when the subject was to determine whether a moving stimulus contained the same directional attribute provided in the preceding cue period. Right parietal lobe damage has also been reported to cause bilateral deficits in high-level apparent motion perception (Battelli et al., 2001). Furthermore, there have been reports of right-hemisphere dominance in the ventral intraparietal area (along the IPS) for the processing of auditory (Hirnstein, Hausmann & Lewald, 2006; Schlack, Sterbing-D'Angelo, Hartung, Hoffman & Bremmer, 2005), visual (Colby, Duhamel & Goldberg, 1993) and tactile (Duhamel, Colby & Goldberg, 1998) motion stimuli in studies of macaque neurophysiology. In fMRI studies with humans, right parietal regions have been shown to be responsive to not only auditory (Griffiths et al., 1998) but also multimodal motion stimuli (Bremmer, Schlack, Duhamel, Graf & Fink, 2001; Bremmer et al., 2001). It has been suggested that right parietal areas are involved in attentional tracking or processing of high-level (multimodal) motion stimuli (Griffiths et al., 1998; Hirnstein et al., 2006).

One might argue that our results may be related to a reduction in mean luminance or contrast with the high-level stimuli relative to the low-level stimuli. Although this might account for some of the reduction in posterior occipital cortex activity, it is unlikely to account for all of the results observed. Firstly, if Dmax was mediated only through a mechanism dependent on contrast, decreasing dot probability (for example) should dampen the input to this mechanism, resulting in a decrease in Dmax, which is not consistent with psychophysical studies. Secondly, BOLD fMRI responses in extrastriate visual areas have been reported to be invariant to changes in luminance contrast (Goodyear & Menon, 1998) with respect to spatial extent of activation as well as to percent change in signal intensity. Even if extra-striate areas were influenced by luminance or contrast, one might expect a greater response with increases in stimulus luminance or contrast. In this study, we observe an increase in response despite the decrease in mean luminance and/or contrast that accompanies the less complex, high-level RDK stimuli.

Models suggesting that first-order RDKs may be biased towards either low- or high-level motion processing depending on stimulus parameters have been debated. This study, to our knowledge, provides the first neuroimaging evidence in support of these models. In addition to the expected increased activation in high-level extrastriate motion areas, there was a consistent and robust decrease in activation in low-level posterior occipital areas for high-level relative to low-level stimuli. Additional studies investigating the trend towards a right hemisphere bias in motion processing and the use of retinotopic mapping in individual subjects will be useful in further defining the neural substrates involved in low- and high-level processing of first-order, random-dot motion stimuli.

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# CHAPTER 5: LOW- AND HIGH-LEVEL MOTION PERCEPTION DEFICITS IN ANISOMETROPIC AND STRABISMIC AMBLYOPIA: EVIDENCE FROM FMRI[1]

## 5.1 INTRODUCTION

Clinically, amblyopia is characterized by reduced visual acuity in one eye despite normal ocular health and optimal refractive correction. In unilateral amblyopia, the fellow (unaffected) eye demonstrates normal visual acuity. In addition to visual deprivation, amblyopia may be caused by strabismus, anisometropia or a combination of both strabismus and anisometropia.

The human visual system comprises at least two parallel neural pathways that are involved in form perception and motion perception. The parvocellular (P) and the magnocellular (M) pathways are responsible for aspects of form and motion processing, respectively. The P pathway projects from the primary visual cortex ventrally to the temporal cortex (Milner & Goodale, 1995; Ungerleider & Mishkin, 1982). The M pathway in the human visual system projects dorsally and includes motion-sensitive extrastriate areas: V3A (Tootell et al., 1997), V5/MT+ (Tootell et al., 1995; Zeki et al., 1991) and regions of the posterior parietal cortex (PPC) (Cheng, Fujita, Kanno, Miura & Tanaka, 1995; Dupont, Orban, De Bruyn, Verbruggen & Mortelmans, 1994; Orban et al., 2006; Sunaert, Van Hecke, Marchal & Orban, 1999).

Psychophysical tests showing visual losses other than reduced visual acuity in amblyopia implicate deficits in both P/ventral and M/dorsal pathways. In addition to reduced visual acuity, there are well-documented deficits in other aspects of spatial vision such as low-contrast acuity, contrast sensitivity, positional acuity and spatial localization (for reviews see Asper, Crewther & Crewther, 2000; Levi, 1991). Evidence for impairment of motion mechanisms in amblyopia has grown since early reports of abnormal temporal processing (Schor & Levi, 1980a, 1980b; Steinman, Levi & McKee,

[1] A version of this chapter has been submitted for publication. Ho, C.S. & Giaschi, D.E. (under review). Low- and high-level motion perception deficits in anisometropic and strabismic amblyopia: Evidence from fMRI. *Vision Research*

1988) and include deficits of oscillatory movement displacement (Buckingham, Watkins, Bansal & Bamford, 1991; Kelly & Buckingham, 1998), motion-defined form (Giaschi, Regan, Kraft & Hong, 1992; Ho, Giaschi, Boden, Dougherty, Cline & Lyons, 2005), motion after-effect (Hess, Demanins & Bex, 1997), maximum motion displacement (Ho et al., 2005; Ho & Giaschi, 2006, 2007), and global motion (Ellemberg, Lewis, Maurer, Brar & Brent, 2002; Simmers, Ledgeway, Hess & McGraw, 2003). There have been numerous reports of abnormal motion perception in the fellow eye suggesting that these deficits are not well accounted for by reduced visual acuity (or other form perception deficits) in amblyopic eyes (Giaschi et al., 1992; Ho et al., 2005; Ho & Giaschi, 2006, 2007; Simmers et al., 2003).

Our recent studies in amblyopia have focused on deficits of maximum motion displacement (Dmax). Dmax is the largest displacement at which the direction of a random-dot kinematogram (RDK) can be reliably discriminated (see Ho & Giaschi, 2006, 2007 for a detailed description). If the displacement is small and all dots are shifted in the same direction (100% coherence), direction discrimination is not difficult because the motion perceived is smooth and continuous. As the displacement approaches the maximum displacement value (Dmax), direction discrimination of the apparent motion is still possible but more difficult because the motion appears to be less coherent. The value of Dmax may be restricted by the receptive field size of low spatial-frequency-tuned motion detectors at a low level of motion processing and/or by the efficiency of spatial feature matching at high levels of motion processing (Nishida & Sato, 1995; Sato, 1998; Snowden & Braddick, 1990). It has been suggested that as dot probability is decreased or dot size is increased, motion processing involves low-level mechanisms to a lesser extent and is biased more toward high-level motion mechanisms (Sato, 1998; Smith and Ledgeway, 2001). There have been reports of deficits in maximum motion displacement (Dmax) for both low-level and high-level RDKs in amblyopia (Ho & Giaschi, 2006; 2007). Our findings confirm that this mechanism “switch” is intact in amblyopia but it is associated with an overall decrease in Dmax thresholds. In a functional MRI study of individuals with normal vision, we used the identical low- and high-level RDK parameters and showed that there was increased activation in extrastriate motion areas (putative V3A, MT+, PPC) and decreased activation in lower-level motion areas (posterior occipital cortex: putative V1/V2) during

direction discrimination of high-level RDKs (decreased dot density & increased dot size) relative to the low-level baseline RDK (Ho & Giaschi, submitted (Chapter 4)). This pattern of cortical activation seems consistent with the proposed high-level processing of less complex high-level RDKs.

Several studies of amblyopia suggest that high-level motion processing is more impaired than low-level motion processing. Simmers and colleagues reported deficits with first- and second- order global motion stimuli (Simmers et al., 2003; Simmers, Ledgeway & Hess, 2005) as well as with translational, rotational, and radial optic flow patterns (Simmers, Ledgeway, Mansouri, Hutchinson & Hess, 2006) in an amblyopic population which the authors suggest implicate areas MT and MSTd. We have previously reported deficits in high-level attentive tracking (Ho, Paul, Asirvatham, Cavanagh, Cline & Giaschi, 2006). The results of these studies implicate extrastriate motion-sensitive areas of the dorsal stream as part of the neural deficit underlying amblyopia. The attentive-tracking deficits seen in amblyopia (Ho et al., 2006) are likely associated with impairment of PPC (to which the dorsal visual pathway projects) because Culham and colleagues identified parietal activation using similar attentive-tracking tasks with functional MRI (Culham, Brandt, Cavanagh, Kanwisher, Dale & Tootell, 1998). Attentive tracking (Cavanagh, 1992) is a high-level motion task that involves feature-matching mechanisms. Attentive tracking and high-level Dmax may share similar or related feature-matching mechanisms given that they involve similar PPC regions (Culham et al., 1998; Ho & Giaschi, submitted (Chapter 4)). Furthermore, the PPC is implicated in high-level motion perception because patients with parietal lesions show deficits in motion perception for high- but not low-level tasks (Battelli et al., 2001).

Although several studies of amblyopia have demonstrated psychophysical deficits suggestive of abnormal feature-matching mechanisms (Ho & Giaschi, 2006, 2007; Ho et al., 2006), there has been no direct neuroimaging evidence to date associating extrastriate motion-sensitive brain areas with these behavioural deficits in amblyopic participants. The aim of this study was to investigate the extent to which the high-level, feature-based motion system (and PPC) is impaired in amblyopia. The RDK stimulus parameters were the same as those used in our earlier studies (Ho & Giaschi, 2006;

2007; submitted (Chapter 4)). We assessed children with strabismic and anisometropic amblyopia and controls on two high-level motion conditions (decreased dot density and increased dot size) as well as a low-level baseline condition (small dots, densely spaced). Given our hypothesis that abnormal neural activity in extrastriate cortex may explain the reported behavioural Dmax deficits, less involvement of dorsal extrastriate areas in amblyopic participants relative to control participants during a direction discrimination task with high-level RDKs (compared to the low-level baseline RDK) was expected.

## 5.2 PARTICIPANTS

### 5.2.1 Control Participants

Four control children were tested, ranging in age from 14 to 16 years (*M* = 15.4 yrs, *SD* = 0.9 yrs). All of the subjects tested were visually mature as Dmax has been shown to reach adult levels between age 7 to 8 years (Parrish, Giaschi, Boden & Dougherty, 2005). All children included had distance and near monocular line visual acuity (VA) equivalent to or better than 6/6 or 0.4 M, respectively (Jose & Atcherson, 1977). Both acuity cut-off values represent letter size with detail of 1 min when measured at 6m and 40cm, respectively. Distance line VA was measured using the Regan 96% contrast letter chart and near VA was measured using the University of Waterloo near vision test card. Stereoacuity, assessed using the Randot Stereotest (Stereo Optical Co., Inc.), was required to be equivalent to or better than 40 sec of arc. Worth 4 Dot (W4D) testing (reviewed in Rutstein & Daum, 1998) was used to test for fusion and scored to give another measure of binocularity. The scoring was as follows:

5 = constant fusion
4 = intermittent fusion with intermittent diplopia
3 = constant diplopia
2 = intermittent suppression
1= constant suppression

All control subjects, when tested in the dark at 1 m, were required to have a score of 5. No control subject had a history of ocular pathology or abnormal visual development.

### 5.2.2 Amblyopic Participants

The subjects were referred from the Department of Ophthalmology at the Children's and Women's Health Centre of British Columbia, and from other local clinics. The ages and clinical details of the amblyopic children are summarized in Table 5.1. The age range of the amblyopic children was between 12 and 15 years. Data were collected from 3 amblyopic children with strabismus (*M* = 14.4 yrs, *SD* = 1.0 yrs) and 4 with anisometropia (*M* = 14.2 yrs, *SD* = 1.1 yrs). To be included in the amblyopic group, there had to be greater than a 1 line difference in VA between the amblyopic and fellow eye in the presence of anisometropia and/or strabismus. For those with a 1 line difference in visual acuity, there had to be a history of occlusion therapy. To be classified as anisometropic in this study, there had to be at least a 1.00 dioptre difference in the spherical equivalent refractive error between amblyopic and fellow eyes. None of the subjects included had eccentric fixation, latent or manifest nystagmus, anomalous retinal correspondence, or oculomotor dysfunction with the exception of strabismus. To avoid the possibility of testing subjects with bilateral amblyopia, the inclusion criteria for the fellow eye were the same as those for the control subjects, described above.

Although 1 of the 3 strabismic children also had anisometropia, they were included in the strabismic subgroup. In psychophysical studies, aniso-strabismic individuals are often classified into "strabismic amblyopia" (e.g. Barnes, Hess, Dumoulin, Achtman & Pike, 2001; Demanins, Wang & Hess, 1999; Mansouri, Allen & Hess, 2005; Mussap & Levi, 1999). Children with strabismus demonstrate different spatial deficits than children with pure anisometropia even if the strabismus is early onset and/or coexists with anisometropia (Birch & Swanson, 2000). In our study, children with stereoacuity less than 500 sec of arc were considered binocular and those with no measurable stereoacuity (>500 sec of arc) on the Randot Stereotest were considered non-binocular. In general, the anisometropic and strabismic groups represented binocular and non-binocular groups, respectively. The average stereoacuity and Worth-4-Dot scores for

**Table 5.1:** Clinical Details for Amblyopic Participants

| | Subject | Age (years) | Decimal VA (amblyopic) | Decimal VA (fellow) | Stereoacuity (sec of arc) | Worth-4-Dot | Refraction | Clinical details & ocular deviation |
|---|---|---|---|---|---|---|---|---|
| **S+A** | A | 13.5 | 0.43 | 1.26 | 500 | 1 | OD: plano<br>OS: +3.25 | Diagnosed age 10; no patching or surgery; 8Δ LXT |
| **S** | B | 14.1 | 1.09 | 1.22 | 500 | 3 | OD: plano<br>OS: plano | Surgery age 9 months; no patching; 6Δ RET |
| **S** | C | 15.5 | 1.09 | 1.26 | 70 | 3 | OD: plano<br>OS: plano | Diagnosed age 3; patching; no surgery; 15Δ LXT |
| **A** | D | 12.9 | 0.89 | 1.15 | 50 | 4 | OD: +4.00+2.50x85<br>OS: +3.75+4.00x11 | Diagnosed age 3; patching;<br>4Δ esophoria |
| **A** | E | 14.1 | 0.73 | 1.03 | 20 | 5 | OD: -1.50<br>OS: plano | Diagnosed age 5; patching; orthophoria |
| **A** | F | 14.1 | 0.55 | 1.19 | 40 | 5 | OD: +6.00+0.50x90<br>OS: +5.50 | Diagnosed age 2; patching; 2Δ esophoria |
| **A** | G | 15.7 | 0.71 | 1.00 | 20 | 5 | OD: +0.25+0.50x63<br>OS: -2.00 | Diagnosed age 3; patching; 8Δ exophoria |

S: strabismus; A: anisometropia; RET: right esotropia; LXT: left exotropia; OD: right eye; OS: left eye; Δ: prism dioptre

the anisometropic group in this study were 33 sec (*SD*=15) and 4.8 (*SD*=0.5). The same scores in the strabismic group were 357 sec (*SD*=248) and 2.3 (*SD*=1.2).

## 5.3 PSYCHOPHYSICS

Prior to the fMRI sessions, individual Dmax thresholds for direction discrimination were determined in the psychophysics laboratory. This was done to equate the difficulty level of the behavioural task in the scanner and to account for the expected variability in Dmax threshold values across subjects. Specifics regarding the stimuli, psychophysical procedures, and threshold calculations are described in detail in our previous paper (Ho & Giaschi, submitted (Chapter 4)). This study followed the exact same psychophysical procedures and methods and a brief description is provided here.

Each subject performed the task under three display parameters in each eye: 20 min dot size at 5% dot density (Condition 1), 20 min dot size at 0.5% dot density (Condition 2), and 1 deg dot size at 5% dot density (Condition 3). The study was approved by the University of British Columbia's Clinical Research Ethics Board. For the fMRI phase of the study, the eyes were dissociated by using red-green filters to allow for monocular testing (see 5.4.1). Use of red-green filters is a standard method for binocular dissociation commonly used in orthoptic evaluation and training. To be consistent, the psychophysical thresholds were determined while the subjects wore the same MRI-compatible glasses with the red-green filters in place such that the right eye viewed through a red filter and the left eye through a green filter. A neutral density filter was used to make the right and left images equiluminant. Prescribed optical correction was worn under red-green filters throughout testing for subjects requiring refractive correction. The non-tested eye was occluded with an opaque patch worn under the corrective/red-green glasses. The eye tested first was randomly varied for each subject.

For each trial, the random dot display was shifted by a given displacement, upward or downward, at 100% coherence, for 10 consecutive frames of animation. The task was direction discrimination of the apparent motion. A two-alternative forced-choice (2AFC) paradigm was used, in which the probability of accurately guessing the correct response

was 50%. As the displacement increased, the task of direction discrimination became more difficult. To ensure that the task was understood before each session, the participants were asked to do a series of practice trials.

All conditions began with a jump size of 0.3 deg that all participants could perform easily with 100% accuracy. For the real trials, jump size was adjusted according to a 2 up 1 down staircase procedure such that it increased after two correct responses and decreased after one incorrect response. The staircase ended after the $15^{th}$ reversal in jump size or after 60 trial presentations, whichever occurred first. Throughout testing, subjects were asked to maintain fixation on a cross in the middle of the screen. Threshold was defined using the stimulus level at which performance was 75% correct, halfway between the guess rate (50% correct) and perfect performance (100% correct) for a 2AFC paradigm. The six thresholds were recorded to be used later in the fMRI scans described below.

Table 5.2 lists the psychophysical thresholds obtained for each subject. As expected, Conditions 2 and 3 (the high-level conditions) gave larger Dmax values than Condition 1 (the baseline low-level condition) in both amblyopic and control groups.

**Table 5.2:** Individual Dmax thresholds (degrees of visual angle) for low-level (Condition 1) and high-level (Conditions 2 & 3) RDKs

| Group | Subject | **Condition 1: *baseline*** (20 min dots at 5% density) | **Condition 2: *decr. dot density*** (20 min dots at 0.5% density) | **Condition 3: *incr. dot size*** (1 deg dots at 5% density) |
|---|---|---|---|---|
| **S** | A | AE: 2.25; FE: 1.26 | AE: 4.32; FE: 4.31 | AE: 4.25; FE: 4.50 |
| | B | AE: 3.41; FE: 2.46 | AE: 4.56; FE: 5.00 | AE: 5.31; FE: 5.90 |
| | C | AE: 1.30; FE: 1.32 | AE: 3.29; FE: 3.20 | AE: 5.25; FE: 4.50 |
| **A** | D | AE: 1.74; FE: 2.00 | AE: 3.75; FE: 4.30 | AE: 4.94; FE: 4.00 |
| | E | AE: 2.25; FE: 3.26 | AE: 4.37; FE 4.39 | AE: 3.41; FE: 3.98 |
| | F | AE: 2.00; FE: 3.31 | AE: 4.00; FE: 3.41 | AE: 5.50; FE:5.00 |
| | G | AE: 1.04; FE: 0.93 | AE: 3.20; FE: 4.36 | AE: 3.25; FE: 3.26 |
| | ***Mean (SD)*** | ***AE: 2.00 (0.77); FE: 2.10 (0.97)*** | ***AE: 3.93 (0.54); FE: 4.14 (0.62)*** | ***AE: 4.56 (0.93); FE: 4.45 (0.84)*** |
| **C** | H | RE: 3.00; LE: 2.75 | RE: 3.32; LE: 4.00 | RE: 4.25; LE: 4.25 |
| | I | RE: 2.33; LE: 2.77 | RE: 4.31; LE: 5.22 | RE: 5.17; LE: 6.00 |
| | J | RE: 1.53; LE: 2.00 | RE: 3.07; LE 3.50 | RE: 6.36; LE: 4.32 |
| | K | RE: 1.25; LE: 1.51 | RE: 3.80; LE: 4.00 | RE: 2.38; LE: 2.75 |
| | ***Mean (SD)*** | ***RE: 2.03 (0.79); LE: 2.26 (0.61)*** | ***RE: 3.63 (0.55); LE: 4.18 (0.73)*** | ***RE: 4.54 (1.68); 4.33 (1.33)*** |

S: strabismic; A: anisometropic; C: control; AE: amblyopic eye; FE: fellow eye; RE: right eye; LE: left eye

## 5.4. FUNCTIONAL MRI

Specifics regarding methods for fMRI data acquisition, visual stimuli and experimental design are described in detail in our previous paper (Ho & Giaschi, submitted (Chapter 4)) and are summarized below.

### 5.4.1 Data Acquisition

Each participant completed a scanning session that lasted approximately one hour. A Philips Gyroscan Intera 3 Tesla MRI scanner with a phased array head coil (SENSE) was used to acquire fMRI data. During a session, echo-planar imaging (EPI) was used to collect functional data in four T2*-weighted scans (TE = 30 ms, TR = 2000 ms, FOV=240 mm, 3 mm isotropic voxels, 80 x 80 mm matrix [reconstructed: 128 x 128 mm matrix, 1.88 x 1.88 mm voxels]). Volumes were collected in 36 interleaved axial slices (3 mm thick, 1 mm inter-slice gap). At the end of each scanning session a high-resolution anatomic brain image was collected with a T1-weighted scan (FOV: 256 mm, matrix: 256 x 256, voxel size: 1 x 1 x 1 mm).

Participants practiced all of the tasks prior to entering the scanner. Equiluminant red and green filters were placed in a MRI-compatible frame with the red filter always in front of the right eye. For those requiring refractive correction, either contact lenses or prescription MRI-compatible lenses were worn under the red-green glasses. Red and green filters, cut from the same filters used in the glasses, were placed over the projector, and changed throughout the scan, to allow for monocular testing. The eye tested first was randomly varied by changing the order in which the red and green filters were placed over the projector.

The visual stimuli were back projected with an LCD projector onto a screen, 53 cm behind the participant's head, and viewed through a mirror that was 15 cm from the participant's eyes. Subject responses were obtained using a fiber optic response system (Lumitouch).

### 5.4.2 Visual Stimuli & Experimental Design

The psychophysical staircase procedures were modified into two different block design fMRI tasks that were run on each eye (for a figure outlining the paradigm see Figure 4.2). Each of the two Dmax runs had six 14 s epochs that were repeated for four cycles. The psychophysical Dmax thresholds for both eyes of each participant were used to determine the jump sizes in each epoch. A total of 6 thresholds were used per subject (3 display conditions x 2 eyes).

The parameters [dot display; dot displacement; motion coherence] for each of the six epochs for the first Dmax run are listed below:

1) 20 min dots at 5% density (Condition 1); Dmax; 100%
2) 20 min dots at 5% density (Condition 1); ½ Dmax; 100%
3) 20 min dots at 5% density (Condition 1); Dmax or ½ Dmax (randomized); 0%
4) 20 min dots at 0.5% density (Condition 2); Dmax; 100%
5) 20 min dots at 0.5% density (Condition 2); ½ Dmax; 100%
6) 20 min dots at 0.5% density (Condition 2); Dmax or ½ Dmax (randomized); 0%

The parameters for the second Dmax run were the same as above for epochs 1-3 but with the following changes for epochs 4-6:

4) 1 deg dots at 5% density (Condition 3); Dmax; 100%
5) 1 deg dots at 5% density (Condition 3); ½ Dmax; 100%
6) 1 deg dots at 5% density (Condition 3); Dmax or ½ Dmax (randomized); 0%

The epochs were presented in the same predetermined randomized order for each run and for every subject. Participants had the task on all trials of pressing one of two buttons to indicate the perceived direction of the apparent motion (up or down) for each trial (even for the random motion trials in which neither was correct). Accuracy of behavioural responses was recorded for each of the coherent motion trials (difficult: dot displacement = Dmax; easy: dot displacement = ½ Dmax) to confirm that level of difficulty and attention to the task were similar across subjects.

### 5.4.3. Data Analysis

Data preprocessing and statistical analysis were conducted with BrainVoyager QX

(Brain Innovation). The preprocessing and whole-brain statistical procedures in this study exactly followed those described in our previous paper (Ho & Giaschi, submitted (Chapter 4). Prior to analysis, inter-slice time differences were removed from the data; corrections were made for small translational and rotational head movements. Temporal high-pass filtering and a linear trend removal algorithm were used to eliminate temporal drifts from the data (e.g. physiological and scanner noise). The functional volumes were co-registered with the anatomic image. The data were then spatially normalized to stereotaxic space (Talairach & Tournoux, 1988) and superimposed onto the respective averaged anatomic images: strabismic, anisometropic, or control for the group analyses.

#### 5.4.3.1 Delineating the motion-selective regions-of-interest

To identify the low- and high-level motion-sensitive regions-of-interest (ROIs), analysis was done both for individual subjects, as well as for each of the three groups. The general linear model was used to analyze the data in a fixed-effects whole brain 3 x 2-factor ANOVA. A boxcar function, convolved with the BrainVoyager default haemodynamic response function (double-gamma function model; Friston et al., 1998) was used to model the data and maps of the *t* statistic were created, with a Bonferroni correction for multiple comparisons ($p<.001$).

The first main effect (Factor A - 3 motion levels: random, easy coherent, difficult coherent) looked at activation differences for direction discrimination of 100% coherent motion with dot displacements of ½ Dmax (easy) and Dmax (hard) relative to random motion (0% coherence) at random displacements. The second main effect (Factor B - 2 RDK levels: high-level, low-level) looked at activation differences between experimental (high-level; conditions 2 and 3) versus the baseline (low-level; condition 1) RDKs. For the ANOVA, the first predictor for each factor (Factor A: random motion; Factor B: low-level condition 1) was excluded and used as the implicit baseline. Factor A x Factor B interactions were also tested.

In all three groups, there was no significant main effect of type of motion (Factor A: coherent motion (for easy or hard direction discrimination) vs. random motion but there was a robust main effect of type of RDK (Factor B: high-level vs. low-level). As

expected based on previous findings (Ho & Giaschi, submitted (Chapter 4)), there was a relative increase and a relative decrease in cortical activity for, respectively, extra-striate high-level parietal and posterior-occipital low-level brain regions when activity obtained with the high-level RDKs was contrasted with that for the baseline low-level RDK. There were no significant interactions.

Table 5.3 lists the brain areas with significant cortical activation differences for the high-level vs. low-level comparison in the strabismic, anisometropic, and control groups. The number of individual subjects from each group showing significant activation in the same brain regions is also presented. Cortical areas with greater than 50 contiguous voxels showing significant differences in activation for all high-level comparisons are listed. The ROIs defined are consistent with those from our previous study of individuals with normal vision (Ho & Giaschi, submitted (Chapter 4)). The posterior occipital ROIs were large in all three groups and included lower visual areas in both hemispheres. The MT+ ROI was the cluster of contiguous activated voxels in the region of the parietal-temporal-occipital junction in each hemisphere. The stereotaxic locations of putative area V3A (e.g. Dupont et al., 1994; Sunaert et al.,1999; Tootell et al., 1997) and MT+ (e.g. Sunaert et al., 1999; Tootell et al., 1995; Zeki et al., 1991) were consistent with locations reported in previous studies. Any parietal cortex activation

**Table 5.3:** Regions-of-interest defined in group analyses: significant cortical activation differences for high-level vs. baseline low-level RDK comparisons (significance level of p<.001 Bonferroni-corrected)

| *Group* | *Group ROI (number of subjects/group with similar ROI)* | | *Hemisphere* | *Extent (mm3)* | *X* | *Y* | *Z* | *Average t-statistic* | *Statistical Threshold* |
|---|---|---|---|---|---|---|---|---|---|
| ***Strabismic*** | **Occipital (2/3)** | | R/L | 1148 | 9 | -77 | 2 | -6.50 | $p<10^{-9}$ |
| | **Putative V3A (0/3)** | | | 0* | | | | | |
| | **MT+ (0/3)** | | | 0* | | | | | |
| | **Parietal (2/3)** | *DIPSM* | R | 18** | 22 | -57 | 57 | +5.70 | $p<10^{-8}$ |
| ***Anisometropic*** | **Occipital (4/4)** | | R/L | 2869 | -6 | -69 | -18 | -7.88 | $p<10^{-10}$ |
| | **Putative V3A (2/4)** | | R | 86 | 23 | -71 | 18 | +6.17 | $p<10^{-9}$ |
| | | | L | 63 | -25 | -68 | 26 | +6.57 | $p<10^{-9}$ |
| | **MT+ (3/4)** | | L | 80 | -44 | -63 | 15 | +6.09 | $p<10^{-9}$ |
| | **Parietal (3/4)** | *POIPS* | R | 282 | 21 | -56 | 36 | +6.23 | $p<10^{-9}$ |
| | | | L | 759 | -20 | -57 | 41 | +6.57 | $p<10^{-9}$ |
| | | *VIPS* | R | 174 | 19 | -64 | 40 | +6.40 | $p<10^{-9}$ |
| ***Control*** | **Occipital (4/4)** | | R/L | 34214 | -1 | -85 | -11 | -12.12 | $p<10^{-10}$ |
| | **Putative V3A (3/4)** | | R | 2343 | 31 | -79 | 16 | +6.33 | $p<10^{-9}$ |
| | | | L | 1293 | -23 | -83 | 17 | +6.24 | $p<10^{-9}$ |
| | **MT+ (3/4)** | | R | 3800 | 40 | -70 | 2 | +6.62 | $p<10^{-9}$ |
| *Cont'd (pg. 120)* | | | L | 2634 | -45 | -76 | 1 | +6.71 | $p<10^{-9}$ |

**Table 5.3:** Regions-of-interest defined in group analyses: significant cortical activation differences for high-level vs. baseline low-level RDK comparisons (significance level of p<.001 Bonferroni-corrected)

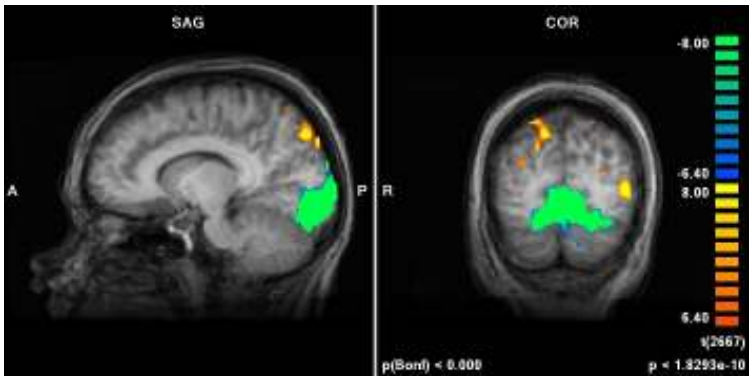
| *Group* | *Group ROI (number of subjects/group with similar ROI)* | | *Hemisphere* | *Extent (mm3)* | *X* | *Y* | *Z* | *Average t-statistic* | *Statistical Threshold* |
|---|---|---|---|---|---|---|---|---|---|
| ***Control** cont'd* | **Parietal (3/4)** | *DIPSM* | R | 992 | 22 | -65 | 50 | +6.53 | $p<10^{-9}$ |
| | | | L | 106 | -16 | -62 | 53 | +5.96 | $p<10^{-9}$ |
| | | *POIPS* | R | 109 | 32 | -58 | 38 | +5.99 | $p<10^{-9}$ |
| | | | L | 76 | -20 | -59 | 46 | +5.89 | $p<10^{-9}$ |
| | | *VIPS* | R | 2589 | 15 | -78 | 38 | +6.83 | $p<10^{-9}$ |
| | | | L | 103 | -17 | -78 | 46 | +6.02 | $p<10^{-9}$ |
| | | | | 174 | -19 | -82 | 33 | +6.11 | $p<10^{-9}$ |

Talairach coordinate system for stereotaxic location: X: right-left Y: anterior-posterior Z: dorsal-ventral
DIPSM: dorsal intraparietal sulcus medial; POIPS: parieto-occipital intraparietal sulcus; VIPS: ventral intraparietal sulcus
ROIs listed above are for cluster sizes > 50 active voxels only (unless otherwise marked): *no active voxels; **no significant ROI cluster > 50 voxels.

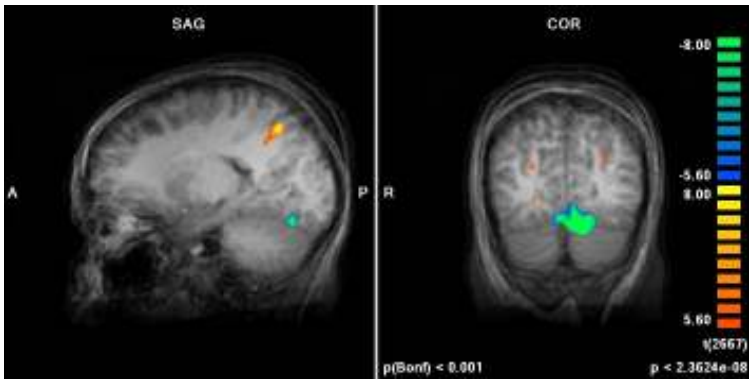
observed was localized to the posterior-dorsal regions of the intraparietal sulcus (IPS) (Dupont et al., 1994; Orban et al., 2006; Sunaert et al., 1999).

Figure 5.1 illustrates the general pattern of cortical activation observed in the control, anisometropic, and strabismic groups for the high-level vs. low-level comparison. The statistical maps are shown on the three group-averaged anatomic images. As expected, a relative decrease in cortical activation in posterior occipital regions and a relative increase in activation in extrastriate motion areas (putative V3A, MT+, and PPC) was observed in the control group when activation for high-level stimuli were compared to that for the low-level RDK. A similar pattern of activation differences was observed in the anisometropic group, although extent of activation was considerably smaller. In the strabismic group, there was relatively little difference in the cortical activation for high-level compared to the baseline with the exception of subtle activation in the posterior occipital ROI. There were no active voxels in areas corresponding to putative V3A and MT+, and very few (<50) contiguous, active voxels in PPC. This suggests that cortical activity in these areas was similar for both high-level and low-level RDKs. A slight right hemisphere bias was noted in the high-level activation regardless of which eye was viewing, which we had also previously observed (Ho & Giaschi, submitted (Chapter 4)).

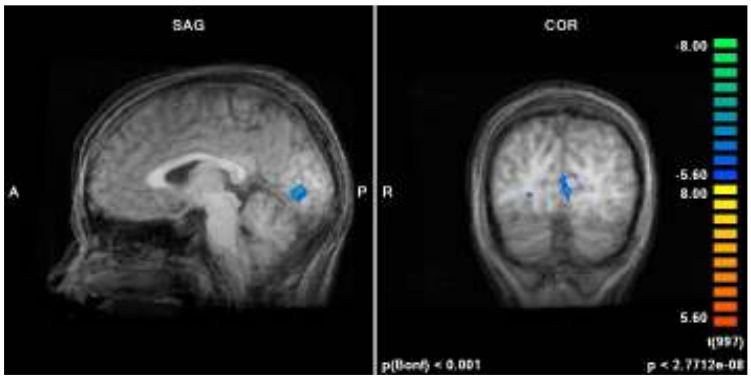
**CONTROL**




**ANISOMETROPIC AMBLYOPIA**




**STRABISMIC AMBLYOPIA**




## Figure 5.1:

Sample sagittal and coronal slices of brain images showing the regions-of-interest used in the ROI analysis (at a significance level of $p<0.001$ with a Bonferroni correction for multiple comparisons). Blue-green colors represent significant negative *t*-statistic values (decreased activation relative to baseline) and red-yellow colors represent significant positive *t*-statistic values (increased activation). ***Top row images*****:** Activation in the control group showing posterior occipital cortex, area MT+, putative V3A (inferior and posterior to activation in PPC), and PPC activation. ***Middle row images*****:** Activation in the anisometropic group. Pattern of activation is similar to controls but extent of activation is significantly less especially in the extrastriate regions. Area MT+ activation is not visible in these slices. ***Bottom row images*****:** Activation in the strabismic group. There is primarily posterior occipital cortex activity. The extent of activation in this ROI is significantly less for this group than in the same ROI for the anisometropic and control groups.

#### 5.4.3.2 Post-hoc region-of interest analyses

**Percent BOLD signal change**

In order to obtain percent blood oxygenation level dependent (BOLD) signal values, a series of group post-hoc contrasts were tested within the ROIs delineated above (occipital, putative V3A, MT+, and parietal areas) for each individual participant (data for both types of high-level RDK was included for each subject). For the post-hoc analysis, the parietal ROI accounted for all active parietal voxels listed in Table 5.3.

Because ROI analyses involve a smaller number of comparisons than whole brain analyses, *t* scores were significant at $p < .05$, uncorrected. Only comparisons of high-level vs. low-level RDKs were investigated post-hoc as this was the only statistically significant effect in the whole-brain ANOVA. Figure 5.2 shows the average percent BOLD signal change obtained within each of the motion-sensitive ROIs for the strabismic, anisometropic, and control groups. In general, putative area V3A, MT+ and parietal ROIs show a significant increase in activation at a significance level of $p=.00$ for every ROI which was consistent across all three groups. The occipital ROI showed a significant decrease in activation for the comparison of high-level vs. low-level with a significance level of $p=.00$ for every ROI in all groups with the exception of the occipital ROI in the strabismic group which was significant at a level of $p<.0005$. Figure 5.3 illustrates the average time course of activation within the occipital and parietal ROIs in the 3 groups across the entire run (164 dynamics/volumes).

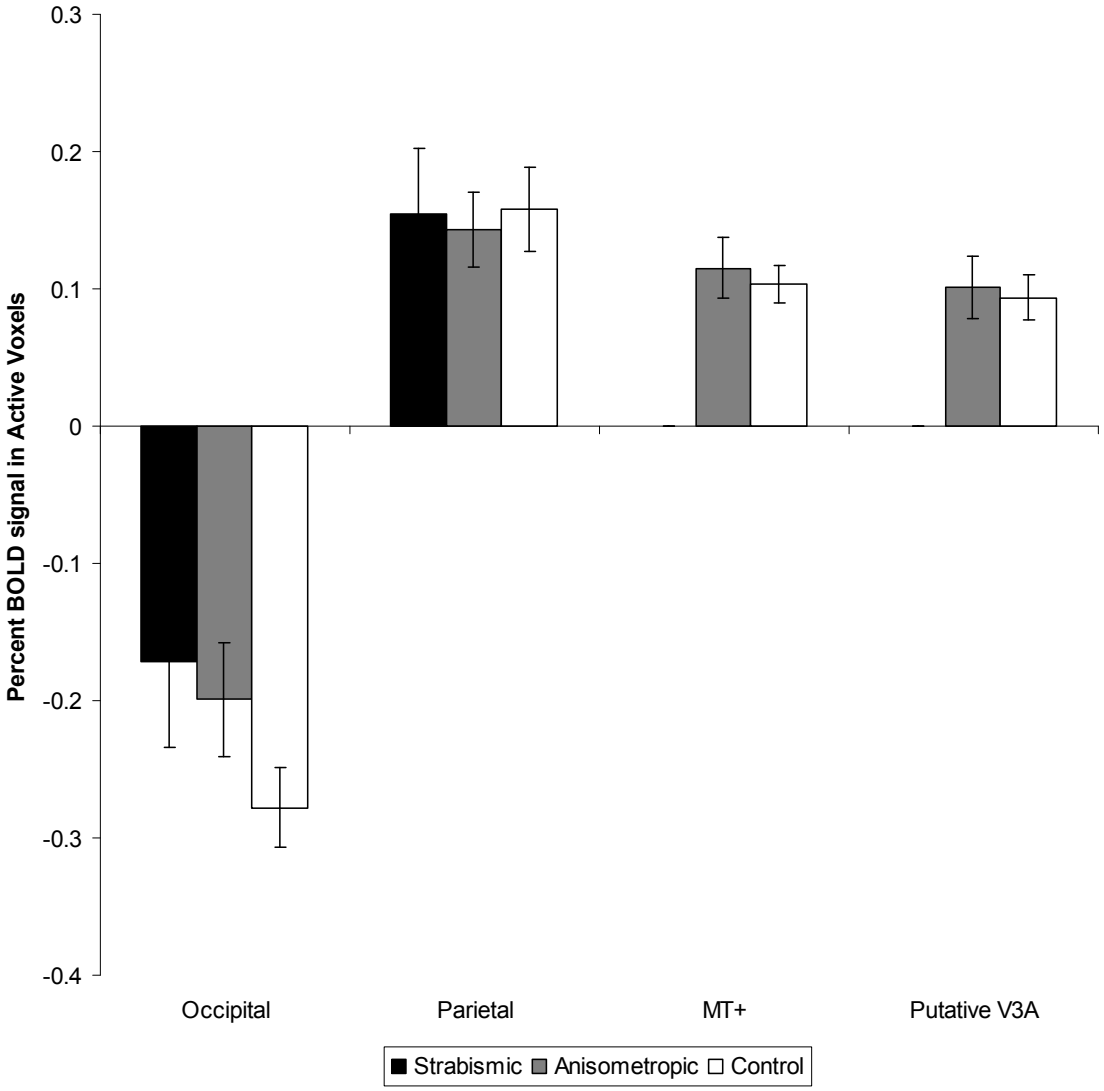



**Figure 5.2:**

Bar graph depicting cortical activation in the 4 ROIs for the comparison of high-level vs. low-level RDK stimuli. The average percent signal change is plotted for each group: control, anisometropic and strabismic. There was a statistically significant decrease in cortical activation for high-level RDKs relative to the low-level baseline RDK in occipital cortex. In contrast, for the same comparison, there was a statistically significant increase in cortical activation in extrastriate motion areas: putative area V3A, MT+, and PPC.

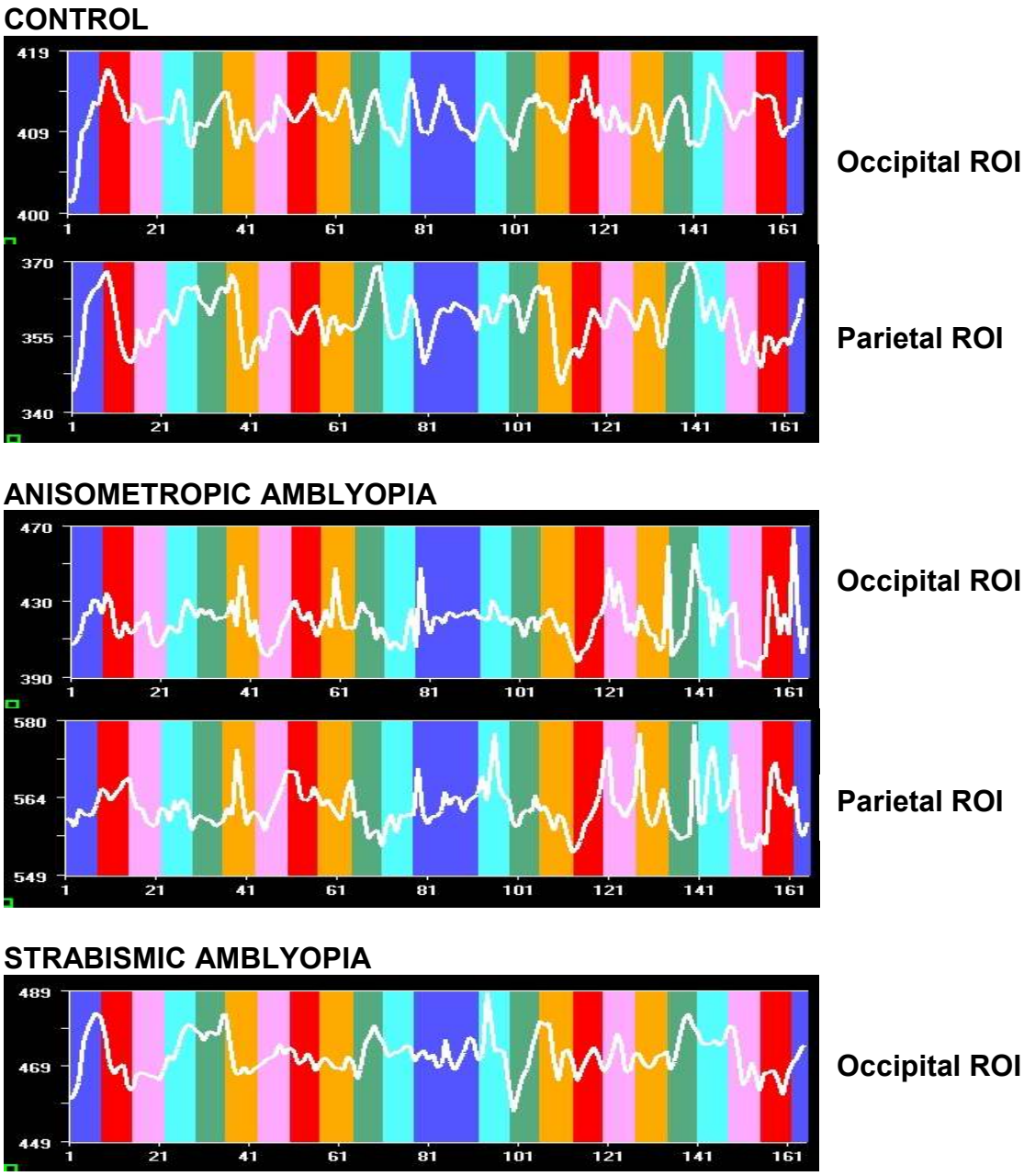



**Figure 5.3:**

Average cortical activation in parietal and occipital ROIs plotted across the time course of entire run (164 dynamics/volumes). Average activation includes that for both high-level conditions. The colored bars correspond to the 6 randomized epoch conditions described in 5.4.2. The order was consistent across all runs for all subjects. Only time courses for ROIs with greater than 50 contiguous voxels are shown. Therefore, there is no data shown for the parietal ROI in the strabismic group.

Table 5.4 shows the frequency of statistically significant percent signal changes relative to the baseline low-level RDK condition across individual subjects in each group. While the findings appear to be quite consistent in the control group, similar to our previous findings (Ho & Giaschi, submitted (Chapter 4)), a decrease in both frequency and consistency was observed for the anisometropic and most notably for the strabismic group.

**Table 5.4:** Individual results for statistically significant percent BOLD signal changes

| *Group* | *Subject* | *ROI* | *Amblyopic eye: High-level (decreased density) vs. Low-level* | *Amblyopic eye: High-level (increased dot size) vs. Low-level* | *Fellow eye: High-level (decreased density) vs. Low-level* | *Fellow-eye: High-level (increased dot size) vs. Low-level* |
|---|---|---|---|---|---|---|
| ***Strabismic*** | **Subject A** | *Occipital* | * | | * | * |
| | | *Putative V3A* | | | | |
| | | *MT+* | | | | |
| | | *Parietal* | | | | |
| | **Subject B** | *Occipital* | | | | |
| | | *Putative V3A* | | | | |
| | | *MT+* | | | | |
| | | *Parietal* | * | | * | |
| | **Subject C** | *Occipital* | | | | |
| | | *Putative V3A* | | | | |
| | | *MT+* | | | | |
| | | *Parietal* | | | | |
| ***Anisometropic*** | **Subject D** | *Occipital* | * | * | * | |
| | | *Putative V3A* | | | | * |
| | | *MT+* | | * | * | * |
| | | *Parietal* | * | * | | |
| | **Subject E** | *Occipital* | * | | | * |
| | | *Putative V3A* | | | * | |
| | | *MT+* | | | * | |
| | | *Parietal* | * | * | * | |
| | **Subject F** | *Occipital* | * | * | * | * |
| | | *Putative V3A* | | * | | * |
| | | *MT+* | * | | | |
| | | *Parietal* | | | | * |
| | **Subject G** | *Occipital* | | | | |
| | | *Putative V3A* | * | | | |
| | | *MT+* | * | | * | * |
| | | *Parietal* | * | | * | |
| ***Control*** | **Subject H** | *Occipital* | * | * | * | * |
| | | *Putative V3A* | * | * | | * |
| | | *MT+* | * | * | | * |
| | | *Parietal* | | * | | |

*Cont'd (pg.128)*

**Table 5.4:** Individual results for statistically significant percent BOLD signal changes

| *Group* | *Subject* | *ROI* | *Amblyopic eye: High-level (decreased density) vs. Low-level* | *Amblyopic eye: High-level (increased dot size) vs. Low-level* | *Fellow eye: High-level (decreased density) vs. Low-level* | *Fellow-eye: High-level (increased dot size) vs. Low-level* |
|---|---|---|---|---|---|---|
| ***Control** cont'd* | **Subject I** | *Occipital* | * | * | * | * |
| | | *Putative V3A* | * | * | * | * |
| | | *MT+* | | * | * | * |
| | | *Parietal* | | * | * | * |
| . | **Subject J** | *Occipital* | * | * | * | * |
| | | *Putative V3A* | | * | * | * |
| | | *MT+* | * | * | * | * |
| | | *Parietal* | * | * | * | * |
| | **Subject K** | *Occipital* | * | * | * | * |
| | | *Putative V3A* | | * | | * |
| | | *MT+* | * | * | * | * |
| | | *Parietal* | | * | * | * |

*denotes that the high-level vs. low-level RDK comparison meets a significance threshold of p<.05 (uncorrected in the ROI analysis)
For the control group, amblyopic & fellow eye columns represent right & left eye results, respectively. (Right & left eyes were randomly selected to act as controls for amblyopic & fellow eyes).

A univariate ANOVA was conducted with the average percent BOLD signal change values obtained for every subject (in each eye, for each ROI) as the dependent variable. Because we were interested in looking at the overall strength of cortical activation in either direction (increase or decrease), the absolute value was used for any negative percent BOLD signal values. The percent BOLD signal change represented any differences in the cortical activity (motion processing) for high-level relative to the baseline low-level RDK. Factors included in the analysis were: brain region (occipital, V3A, MT+, PPC); eye (fellow/right; amblyopic/left); group (strabismic, anisometropic, control); and high-level condition (increased dot size, decreased dot density). There were no significant interactions. Significant main effects of brain region ($F_{(3, 1424)}$=284, $p$=.00), and group were obtained ($F_{(2, 1424)}$=6137, $p$<.0005). There was no significant main effect of eye ($p$=.58) or high-level condition ($p$=.16). Bonferroni multiple comparisons showed that overall strength of cortical activation was greater in the occipital ROI ($M$=0.23%, $SD$=0.15%) than PPC ($M$=0.16%, $SD$=0.12%; $p$<.01), MT+ ($M$=0.09%, $SD$=0.07%; $p$=.00), or putative V3A ($M$=0.08%, $SD$=0.07%; $p$=.00) ROIs. Within the extrastriate ROIs, activation was greater in PPC than MT+ ($p$=.01) and putative V3A ($p$<.005); and activation was similar for MT+ and putative V3A ($p$=1.00). Strength of activation was significantly less in the strabismic group ($M$=0.09% $SD$=0.15% than the anisometropic ($M$=0.15% $SD$=0.10% $p$<.05) and control ($M$=0.16%, $SD$=0.12%; $p$<.005) groups. There was no significant difference in strength of percent BOLD signal change between anisometropic and control groups ($p$=1.00).

**Extent of activation**

The total number of active voxels obtained for the comparison of high-level vs. low-level RDKs (at a level of $p$<.001, Bonferroni corrected for multiple comparisons) was tabulated from the individual whole-brain statistical maps created for every participant (data from each eye analyzed was separately). To look at the overall extent of cortical activation relative to the low-level RDK baseline, the total number of active voxels included those from all brain regions for data from each eye. Figure 5.4 illustrates the total number of active voxels averaged across subjects for amblyopic and fellow eyes (controls: right and left eyes, respectively) in strabismic, anisometropic, and control groups. Although the group data summarized in Table 5.2 imply there are fewer active voxels in the strabismic group than the anisometropic or control groups, calculating the

total number of active voxels with individual statistical maps showed that there were actually slightly more active voxels in the strabismic than the anisometropic group. The difference in number of active voxels represented differences in cortical activation primarily in the posterior-occipital brain regions and not in the extra-striate cortex. This is highly suggestive of decreased activity in lower visual areas such as V1 in amblyopia but does not exclude the possibility of extrastriate deficits. Because there were no active voxels in the individual statistical maps of the group with strabismic amblyopia it is possible that extrastriate deficits exist also, although they did not contribute to the data depicted in Figure 5.4. Despite a slight difference in number of active voxels between the anisometropic and strabismic groups, both groups show a considerable reduction relative to the control group.

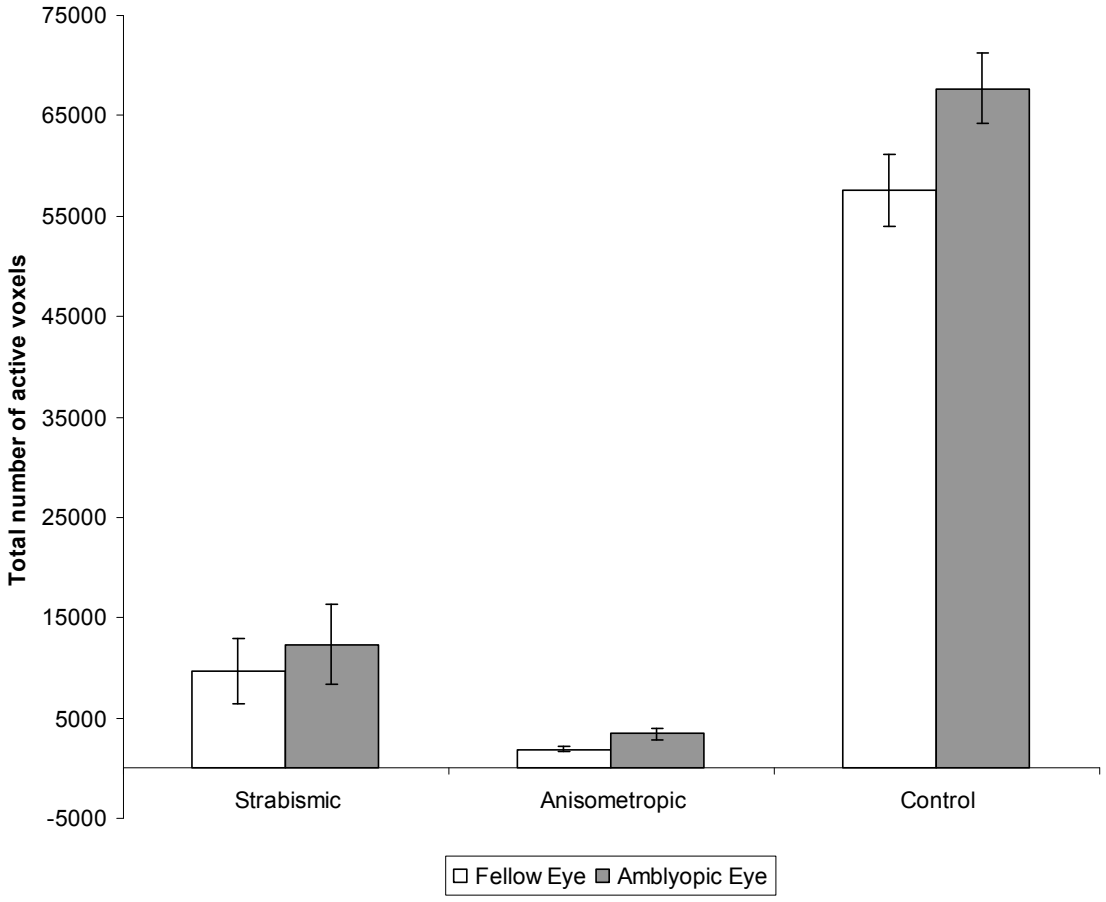



**Figure 5.4:**

Bar graph depicting extent of cortical activation in the 4 ROIs for the comparison of high-level vs. low-level RDK stimuli. The bars represent the average "total number of active voxels" calculated from the statistical map obtained for each individual subject (i.e. not from the group analysis). Data for fellow and amblyopic eyes are shown separately. Performance did not significantly differ between the two eyes. In the control group, the amblyopic and fellow eyes represent the right and left eyes, respectively.

The extent of cortical activation is substantially greater in the control group than in either amblyopic group. A univariate ANOVA with total number of active voxels as the dependent measure and factors of group (strabismic, anisometropic, and control) and eye viewing (fellow/right, amblyopic/left) confirmed the significant group difference ($F_{(2, 170)}$=226, $p$=.00) shown in Figure 5.4. There was no significant difference between eyes ($p$=.11) nor was there a significant interaction ($p$=.34). Bonferroni multiple comparisons indicated that there was a significant difference in overall extent of activation between the control group and the anisometropic ($p$=.00) as well as the strabismic ($p$=.00) groups, but not between anisometropic and strabismic groups ($p$=.48).

**Correlation analysis**

Correlations (N=176) between percent signal change (absolute values), stereoacuity, and W4D scores were tested in addition to correlations between number of active voxels, stereoacuity, and W4D. The 176 data points in the correlational analyses represented percent BOLD signal or number of active voxels obtained with each of the two high-level RDK stimuli (for each eye, in each of the 4 ROIs) for every individual subject. W4D scores (higher scores indicate better binocular function) were only slightly correlated to percent BOLD signal ($r$=0.15) and moreso to extent of activation ($r$=0.31, $p$=.00). Stereoacuity (smaller disparities indicate better binocular function) was also correlated to extent of activation ($r$=-0.25). Because the data involve repeated measures, conclusions based on inferential statistical analysis of the correlations can not be reliably made. Although these correlations are small, they do imply that there may be fewer differences in cortical activation for high-level relative to low-level RDK stimuli when binocularity is compromised. In other words, motion processing of high-level and low-level RDKs may involve (or lack) a common mechanism when binocularity is compromised. For those with uncompromised binocular vision, high-level and low-level RDKs seem more likely to involve different motion mechanisms given that there are more cortical activation differences seen relative to baseline.

## 5.5 DISCUSSION

Decreasing dot density and/or increasing dot size of first-order, luminance-defined RDKs create a bias towards high-level motion mechanisms (Sato, 1998; Smith &

Ledgeway, 2001). In agreement with this, our results show a decrease in activation within lower-level areas (posterior occipital cortex) with high-level (decreased dot density or increased dot size) RDKs relative to the low-level baseline in strabismic, anisometropic and control groups. For the same comparisons, we also found the expected increase in activation in putative area V3A, area MT+, and posterior parietal regions of the IPS in the control and anisometropic groups but not for the strabismic group. The posterior IPS regions involved are consistent with brain areas previously implicated in high-level motion processing in humans (Claeys, Lindsey, De Schutter & Orban, 2003; Culham et al., 1998; Dupont et al., 1994; Ho & Giaschi, submitted (Chapter 4); Sunaert et al., 1999). Despite involvement of similar PPC regions, the results show significant differences in the motion processing of low-level and high-level first-order RDKs between the control and amblyopic groups. Specifically, overall extent of activation was less in strabismic and anisometropic groups relative to controls but did not differ between the two amblyopic groups. The group differences were most pronounced in high-level extrastriate areas. Strength of the percent BOLD signal change (increase or decrease) relative to baseline was greatest in the anisometropic and control groups and significantly less in the strabismic group.

Numerous fMRI studies (Lerner et al., 2003, 2006; Muckli et al., 2006) have shown reduced activation at higher-level areas of the ventral stream in amblyopic individuals. The general trend was for the extent of deficits to increase progressively from lower visual areas to higher visual areas. Extrastriate deficits were most pronounced with amblyopic eye viewing and no significant difference was observed in the cortical activation pattern for anisometropic and strabismic amblyopia. The current findings suggest that high-level areas of the dorsal stream are also impaired to a greater extent than low-level areas in amblyopia. There was a noticeable difference in extrastriate cortical activation between amblyopic and control groups regardless of which eye was viewing. This is not surprising given that psychophysical Dmax thresholds are equally deficient in fellow and amblyopic eyes (Ho et al., 2005; Ho & Giaschi, 2006, 2007). Additional psychophysical evidence implicating high-level dorsal stream dysfunction in amblyopia includes deficits in attentive motion tracking (Ho et al., 2006), underestimation in visual object enumeration (Sharma, Levi & Klein, 2000), and a prolonged attentional blink (Asper, Crewther & Crewther, 2003), all of which involve

PPC ((Culham et al., 1998 (attentive tracking); Marios, Chun & Gore, 2000 (attentional blink); Sathian et al., 1999 (enumeration)).

### 5.5.1 Stimulus considerations

The differences in extent of activation and percent BOLD signal change are not likely accounted for by variability in task performance across the groups. Behavioural responses were tracked and accuracy of direction discrimination was approximately 70 percent correct for all subjects. The fMRI stimuli used also considered the reduced visual acuity of the amblyopic participants. The stimuli were of high contrast (white dots on a black background). The central white fixation cross was large enough to be visible to even those participants with significantly reduced best-corrected visual acuity. The smallest dot size used was 20 min which is equivalent to the minimum angle of resolution of a 6/120 optotype (equal to decimal visual acuity of 0.05).

The pattern of cortical activation observed may be related to the reduction in mean luminance or contrast with the less complex high-level stimuli relative to the low-level stimuli. Although this might account for some of the reduced activity in low-level occipital areas, it is not likely a significant contributor to the overall effects reported. First, if Dmax was mediated through a mechanism dependent only on contrast, decreasing dot probability (for example) would result in a decrease in Dmax, which is inconsistent with psychophysical findings of an increase in Dmax. Secondly, if extrastriate areas were influenced primarily by luminance or contrast, a stronger BOLD response might be expected with an increase, not a decrease, in stimulus luminance or contrast (Logothetis, Pauls, Augath, Trinath & Oeltermann, 2001). We report an increased response in PPC despite the decrease in mean luminance that accompanies the less complex, high-level RDK stimuli. Other studies have reported that BOLD fMRI responses in extrastriate visual areas are invariant to changes in luminance contrast (Goodyear & Menon, 1998) with respect to spatial extent of activation as well as to percent change in signal intensity. Thus, mechanisms other than those which are luminance-dependent are likely responsible for the pattern of cortical activity observed.

### 5.5.2 The role of eye movements

Bedell & Flom (1985) reported bilateral oculomotor abnormalities in strabismic individuals with amblyopia. While it is possible that abnormal eye movements and fixation in fellow or amblyopic eyes could contribute to the different results for the strabismic group, this seems unlikely to be the case. First, none of our subjects had eccentric fixation. Second, to minimize the influence of horizontal eye movements (nasal drifts or asymmetric pursuits) in the direction discrimination task, RDK motion was deliberately chosen to be in a vertical direction. As dot displacement approaches Dmax, stimulus speed also increases, and the task becomes more difficult. Theoretically, children would perceive direction of motion as oblique rather than vertical for larger dot displacements (Souman, Hooge & Wertheim, 2005) due to interference from horizontal eye movements. This would make the task of vertical direction discrimination more difficult and performance would be expected to be worse. However, this is not the case with this sample of strabismic subjects. In fact, the Dmax thresholds were occasionally greater than that obtained in control and anisometropic participants (Table 5.2).

### 5.5.3 Relationship to binocularity

McKee and colleagues (McKee, Levi & Movshon, 2003) found level of residual binocularity to be a better indicator of psychophysical performance than the type of amblyopia. Using RDK stimuli similar to that used in this study, amblyopic children with poor stereoacuity tended to have increased Dmax thresholds relative to those with normal stereoacuity (Ho & Giaschi, 2007). This was true for anisometropic and strabismic amblyopia. The strength of correlation was greatest within the strabismic group and most noticeable for RDKs biasing the high-level motion system for both groups. High-level motion processing relies on feature matching mechanisms such that fewer false-matches should give higher Dmax values. Although amblyopic children demonstrate psychophysical deficits in both low-level and high-level motion mechanisms compared to control children, the high-level, feature-matching mechanism may be relatively spared when fine stereopsis is absent (Ho & Giaschi, 2007).

In this study, poor binocular function was significantly associated with a smaller extent of activation overall (and to a lesser degree, reduced strength of BOLD signal). The

strabismic (non-binocular) group showed almost no difference in cortical activation between low-level and high-level RDK stimuli, particularly in extrastriate areas. This could be possible if both types of RDK stimuli were processed by a common mechanism. Taken together with the psychophysical Dmax findings, it seems plausible that the strabismic children may use high-level correspondence mechanisms even for low-level RDK stimuli. Dmax for direction discrimination and Dmax for disparity detection are similar in value (Glennerster, 1998) suggesting some overlap between correspondence mechanisms for motion and depth perception. It is of interest also that others (McColl, Ziegler & Hess, 2000; Wilcox & Hess, 1995) have reported on the persistence of a coarser-scaled, non-linear stereopsis mechanism despite deficits in finer-scaled, linear stereopsis mechanism. Wilcox and Hess suggested that the coarser-scaled disparity mechanism may benefit correspondence mechanisms by possibly reducing the probability of false-matches, improving detection of object features as well as minimizing diplopia.

### 5.5.4 Etiological differences

Despite the different patterns of activation in extrastriate cortex across the groups, there was a consistent activation decrease in lower-level occipital areas with high-level RDKs relative to low-level RDKs for strabismic, anisometropic, and control participants. The extent of occipital activation was markedly less in the strabismic and anisometropic groups than the control group. This reduction in neural activity in lower-level areas for strabismic and anisometropic groups might be responsible for the reduced activation in extrastriate cortex. However, it can not be ruled out that decreased feedback from extrastriate cortex may be responsible for the findings in posterior occipital cortex. V1 activity is mediated by feedback from MT+ in the perception of long-range (high-level) apparent motion (Sterzer, Haynes & Rees, 2006). Active high-level motion mechanisms are associated with increased neural activity in PPC or MT+ which may provide important feedback to inhibit low-level occipital areas. This might be a fundamental neural process present in both amblyopic and control groups (although possibly more effective in the control group) that increases efficiency of high-level motion mechanisms by reducing competitive neural activity from low-level motion mechanisms.

It has been theorized that strabismic amblyopia may be associated with decreased synchronization of functional neurons (Roelfsema, Konig, Engel, Sireteanu & Singer, 1994). Decreased neural activity in extrastriate cortex may be a result of neural asynchrony (Anderson, Holliday & Harding, 1999; Anderson & Swettenham, 2006). The extent or strength of neural input into (rather than neural output or frequency of synaptic firing from) a specific brain area has been reported to be closely associated with the BOLD response observed in that area (Logothetis et al., 2001; Logothetis, 2002)). Therefore, the lack of activation difference in extrastriate cortex of the strabismic group could be explained by a lack of input to high-level motion-sensitive areas. This hypothesis, however, is inconsistent with psychophysical findings which suggest that high-level mechanisms may be spared in strabismic (non-binocular) amblyopia. If high-level mechanisms were used for both low-level and high-level RDKs, there would also be no significant activation difference observed in extrastriate areas. Therefore, the lack of a cortical activation difference in high-level areas might not truly reflect an extrastriate deficit. Strabismic amblyopia has been associated with neural miswiring of receptive fields tuned to a normal range of spatial frequencies (Hess, Field & Watt, 1990; Kiorpes & McKee, 1999). This miswiring might restrict the spatial extent of larger motion detectors, or create a confusing low-level motion signal. Thus, increased reliance on high-level feature-matching for motion discrimination may have a compensatory role.

### 5.5.5 General conclusion

We observed a decrease in extent of overall activation and strength of BOLD signal in extrastriate motion-sensitive areas of anisometropic and strabismic groups relative to controls. The extrastriate deficits appeared larger for the strabismic group than the anisometropic group when activation for high-level RDK stimuli was compared to the baseline low-level RDK. These cortical deficits may be explained by a progressive degradation of neural signals in the dorsal pathway such that neural input to target high-level motion-sensitive cortex is weakened. However, this explanation for the strabismic (non-binocular) group is contrary to behavioural evidence supporting a relative sparing of correspondence mechanisms associated with poor stereoacuity (Ho & Giaschi, 2007; McColl et al., 2000; Wilcox & Hess, 1995). An alternative hypothesis for the decreased BOLD signal observed in extrastriate cortex of the non-binocular (strabismic) group for

high-level vs. low-level comparisons, is a predominance of high-level, feature-matching mechanisms (over low-level mechanisms) in motion processing for *both* low-level and high-level RDK stimuli. Future studies will explore these two contradictory theories with larger sample sizes so that cortical activation patterns observed in this study can be confirmed through random effects analysis.

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# CHAPTER 6: CONCLUSIONS & DIRECTIONS FOR FUTURE RESEARCH

The studies in this thesis were intended: 1) to characterize deficits in low-level and high-level Dmax for direction discrimination in the fellow and amblyopic eyes of participants with anisometropic and strabismic amblyopia; and 2) to investigate the relationship between psychophysical Dmax deficits and dysfunction of the extrastriate cortex of the M/dorsal stream.

## 6.1 DISCUSSION OF PSYCHOPHYSICAL STUDIES

### 6.1.1 Summary & Implications: Psychophysics

The hypothesis tested in the psychophysical studies was that strabismic children with amblyopia would have greater psychophysical Dmax deficits relative to control children and anisometropic children with amblyopia. This was based on evidence suggesting that extrastriate deficits may be more pronounced in strabismic relative to anisometropic amblyopia (Kiorpes & McKee, 1999). Consistent with the hypothesis, the results from Chapters 2 and 3 confirm that Dmax thresholds for the anisometropic and strabismic groups with amblyopia were significantly lower (i.e. indicating worse performance) than in the control group. The strabismic group showed deficits to a greater extent than the anisometropic group when performance was compared to that of the control children. However, performance was not always significantly different between the two amblyopic groups. The deficits also did not differ between amblyopic and fellow eyes; which is of importance because it implicates motion-sensitive regions with strong binocular input. Because performance in amblyopic and fellow eyes is similar, this suggests that Dmax thresholds may be associated with abnormal binocular connectivity more so than a loss of monocular neurons or spatial deficits in the receptive field properties of monocular neurons. Furthermore, because deficits between the two groups were not robustly different, binocular status and not subtype of amblyopia may be more useful in predicting the existence of motion deficits.

In fact, there was a robust correlation between poor stereoacuity and high Dmax, especially for the high-level version of the RDK stimuli (mediated by feature-matching mechanisms). A surprising finding was that those showing the most impairment in

binocular integration had higher Dmax thresholds, which seems contradictory to what one might expect. Visual acuity, in contrast, was not a good predictor of the extent of Dmax deficits. Although both groups of amblyopic children had deficits in Dmax, within both anisometropic and strabismic groups, those with better stereoacuity tended to have smaller Dmax thresholds than those with worse stereoacuity. Children with measurable stereoacuity must have binocular neurons capable of integrating visual input from each eye but the smaller Dmax thresholds may represent abnormalities in the binocular interaction or competition relative to children with normal visual systems.

The lack of binocular integration in children with no measurable stereoacuity appears to be an advantage for high-level motion processing which involves tracking the movement of object features. Dmax for motion perception and Dmax for stereopsis are similar in value (Glennerster, 1998). Therefore, it is possible that children with increased Dmax for motion may also have larger Dmax for stereopsis and be able to fuse large (coarse) disparities, despite an inability to fuse fine disparities. This suggests that there may be common correspondence mechanisms for large disparities and for motion perception. It also introduces the possibility of a relative sparing of coarse-scaled stereopsis mechanisms in amblyopic children who fail clinical tests of stereoacuity. In fact, these "non-binocular" children may have some degree of residual binocularity that is not detected with standard clinical tests. The presence of a coarse-scaled stereopsis mechanism in strabismic amblyopia (despite the absence of a fine-scaled stereopsis mechanism) has been proposed to possibly improve efficiency of feature-matching and to minimize diplopia (Wilcox & Hess, 1995). This may be of benefit to strabismic subjects who have a history of ocular misalignment. Furthermore, it may reflect abnormal organization of the binocular connections, possibly with increased spatial extent of lateral interactions for strabismic amblyopia. It could also represent the possibility that binocular connections within brain regions of the M/dorsal stream are stronger than those within the P/ventral stream for strabismic amblyopia; or a relative sparing of the M/dorsal stream. This is a feasible explanation since the lack of stereoacuity (fine disparity detection) may implicate a deficit in the P/ventral stream which has receptive field properties that are sensitive to stimuli of a finer-scale relative to the M/dorsal stream (discussed in Ho & Giaschi, 2007 (Chapter 3)). Moreover, the neurophysiological connection between Dmax for stereopsis and Dmax for motion is

believed to be extrastriate brain area MT+ in the dorsal stream (Neri, Bridge & Heeger, 2004; Uka & DeAngelis, 2006).

### 6.1.2 Limitations & Future Directions: Psychophysics

Because this series of experiments did not directly test coarse stereopsis, this is an area that warrants further study. It would be especially interesting to explore the relationship between Dmax for stereopsis and Dmax for motion direction discrimination in amblyopic individuals who are classified according to their fine stereoacuity measures. In general, for all of the studies presented within this thesis, the binocular group was anisometropic and the non-binocular group was strabismic. Hence, there is still some ambiguity as to whether the results observed are due to etiological differences or due to variations in binocular status. In theory, it would be most appropriate to investigate a group of children with only one subtype of amblyopia (either strabismic or anisometropic) that have stereoacuity measures over a wide range of disparities. That would provide the most convincing evidence of a relationship between binocularity and correspondence mechanisms (i.e. between coarse-scaled stereopsis and motion direction discrimination) by eliminating the possibility of the results being due to etiological differences. However, given that clinical histories can vary widely across patients, obtaining strabismic and anisometropic groups (with sufficiently large sample sizes) that meet the above criteria may pose somewhat of a challenge.

## 6.2 DISCUSSION OF NEUROIMAGING STUDIES

### 6.2.1 Summary & Implications: fMRI

It was hypothesized that the pattern of cortical activation when comparing activity for high-level relative to low-level RDKs, would differ between control participants and those with anisometropic and strabismic amblyopia based on the psychophysical findings. Whether a difference in activation pattern between the two types of amblyopia would be observed was uncertain given that other researchers have found no difference in extrastriate activity of the ventral stream between anisometropic and strabismic amblyopia (Muckli, Kiess, Tonhausen, Singer, Goebel & Sireteanu, 2006; Lerner et al.,

2003, 2006). However, there was a robust correlation between psychophysical Dmax thresholds and stereoacuity in Chapter 3, which might predict a cortical activation difference for anisometropic (binocular) and strabismic (non-binocular) amblyopia. In either case, because Dmax deficits implicate involvement of extrastriate cortex, it was expected that any cortical differences in neural activity would be most noticeable in extrastriate regions of the M/dorsal stream. Indeed, the results of the fMRI study confirmed this expectation and also made apparent a cortical activation difference between strabismic and anisometropic ambloypia.

When comparing cortical activation for high-level relative to low-level motion processing in normal observers, there was a decrease in the BOLD response in the low-level, posterior occipital visual areas and increase in activity in high-level, extrastriate occipital and posterior parietal areas of the M/dorsal stream. This is suggestive of decreased low-level processing and increased high-level processing for the high-level stimuli. The high-level stimuli were luminance-defined (first order) RDKs of reduced dot density and increased dot size. The low-level baseline stimulus was a first-order RDK of small, densely spaced dots. There has been much controversy as to whether the first-order RDKs with reduced dot density and/or increased dot size actually involve feature-matching motion mechanisms. The control results, taken alone, are significant because they provide the first reported neuroimaging evidence confirming that motion processing for first-order RDKs can be mediated by either low-level or high-level motion mechanisms depending on the stimulus parameters chosen.

The pattern of activation in occipital and parietal cortex was similar for the group with anisometropic amblyopia relative to the control group although extent of activation and strength of BOLD signal was significantly less. The pattern of cortical activity in the strabismic group did not parallel that of the anisometropic group. In fact, the strabismic group did not show a difference in extrastriate activation for the low-level and high-level RDK stimuli. This suggests that a common mechanism is engaged for both types of RDKs since the low-level RDK stimulus was used as the baseline for the fMRI comparison. The results could suggest an extrastriate deficit in which high-level mechanisms are deficient and low-level mechanisms are active for both types of RDKs. However, taken in conjunction with the psychophysical results suggesting a relative

sparing of motion correspondence mechanisms with strabismic amblyopia, an alternate possibility is that low-level mechanisms are deficient and that high-level, correspondence-based motion mechanism are active for both types of RDKs. Consistent with the trend in the psychophysical results, there was a significant correlation between stereoacuity and extent or strength of cortical activation. Specifically, extent and strength of the BOLD response was greater for those with better stereoacuity. This implies that there is a greater distinction between low-level and high-level motion processing in individuals with the ability to discriminate fine disparities (for the RDK stimuli specific to this study).

### 6.2.2 Limitations & Future Directions: fMRI

Additional studies will be necessary to differentiate whether deficiencies in low-level or high-level motion processing mechanisms are responsible for the reduced extrastriate activity observed in the group with strabismic amblyopia. It may be useful to determine the extent of high-level motion processing deficits by investigating cortical activation patterns for a different high-level motion task such as attentive tracking which has been shown to be deficient in amblyopia (Ho, Paul, Asirvatham, Cavanagh, Cline & Giaschi, 2006). Attentive tracking has been shown to activate similar regions of the PPC as those identified in the current study. If strabismic amblyopia is associated with a relative sparing of high-level motion mechanisms then activation in the PPC may be more similar to controls than those with anisometropic amblyopia when comparing activation for attentive tracking vs. passive viewing of a moving stimulus. It would also be beneficial to include a larger number of subjects within each subgroup of amblyopia so that a general linear model analysis based on random effects could be done. This would provide stronger results that could be better generalized to the amblyopic populations, unlike the results of the fixed effects analysis done in this study which applies only to the sample of subjects tested.

Retinotopic mapping is a method of delineating borders between visual areas in the occipital cortex. The borders can be identified by using stimuli presented at vertical and horizontal meridians (for overview see Tootell, Hadjikhani, Mendola, Marrett & Dale, 1998). The retinotopic brain regions superior to the calcarine sulcus are (moving

dorsally): V1, V2, V3, V3A, and V7. Inferior to the calcarine sulcus, the retinotopic brain regions are (moving ventrally): V1, V2, VP, V3V, and V8. The borders of the visual areas may be mapped with fMRI using vertically and horizontally oriented visual stimuli, usually filled with a flickering checkboard pattern that maximally stimulates lower visual areas. The vertical meridian maps the borders between: area V1 and V2 both superior and inferior to the calcarine sulcus; dorsal areas V3 and V3A; and ventral areas VP and V3V. The horizontal meridian maps the borders between: dorsal areas V2 and V3; V3A and V7 and ventral areas V2 and VP; V3V and V8. Use of this technique would allow for more detailed understanding of the cortical activation obtained in the posterior-occipital cortex. It would reduce dependence on Talaraich coordinates (Talaraich & Tournoux, 1988) or on sulcal landmarks when drawing conclusions about activation in the occipital cortex. Instead it would be possible to functionally define the regions and make more meaningful comparisons across individual subjects. The lower visual areas showing reduced cortical activation for high-level relative to low-level motion stimuli in this study comprised a region-of-interest sufficiently large to likely encompass V1 and V2 but this could be confirmed by combining the statistical maps for the Dmax comparisons with results from retinotopic mapping. Furthermore, activation in an area corresponding to V3A (as described in other papers) is discussed throughout this thesis as activation in extrastriate area “putative V3A”. V3A is functionally defined and can only be accurately localized with retinotopic mapping (Tootell et al., 1997). Therefore, to make definitive conclusions regarding area V3A, retinotopic mapping would be necessary. This thesis investigated *general* differences in patterns of neural activation for low-level (striate cortex) and high-level (extra-striate) motion processing in control and amblyopic children. Future studies will extend these findings by characterizing in greater detail the activation in functionally-defined visual areas of the M/dorsal stream. Regrettably, there is no reliable method of functionally defining high-level extrastriate areas in PPC.

Although standard fMRI analysis provides some information on neural activity with high spatial resolution it has poor temporal resolution and is not an effective technique to provide detailed information on the timing of neural activity or the connectivity of active brain regions. Diffusion tensor imaging (DTI) is a relatively new MRI technique that can provide information about the myelinated fibres connecting different brain regions by

providing in vivo details on white matter tracts (Jones, 2005; Pierpaoli, Jezzard, Basser, Barnett & Di Chiro, 1996). Axons travel in parallel bundles and diffusion does not penetrate the myelinated membrane. Therefore, water diffusion is generally along the direction of the fibre tract and not perpendicular to it. This creates anisotropy in the direction of diffusion which is the basis for DTI tractography images. The images obtained with tractography allow one to visualize the location and orientation of the brain's white matter tracts that form the connections between gray matter areas of the brain. A very recent study has used DTI tractography to identify neural deficits in the optic radiations (projections from the lateral geniculate nucleus to V1) in amblyopic children with mixed etiologies (Xie et al., 2007). The authors concluded that the optic radiations in amblyopia may be underdeveloped relative to controls and suggest that this may be due to abnormal postnatal myelination of axonal tracts early in the visual system which appears to be independent of etiology.

During the processes of brain maturation, total water content decreases and myelination increases. These changes that occur with normal maturation also create changes in water diffusion properties. Although not as commonly studied, gray matter can also be studied with DTI because it has different diffusion properties than white matter (Liu, Li, Wong, Tarokh, Guo & Wong, 2007). This makes DTI a useful tool for not only tractography but also for comparing brain structure in those with developmental disorders to those with normal development (Hermoye et al., 2006; Filippi et al., 2003). Developmental brain disorders may show abnormalities in the magnitude of anisotropy and detecting these differences could aid in localizing neural deficits associated with the disorder.

DTI studies might be helpful in clarifying the nature of the observed cortical extrastriate deficit in the strabismic group. By using tractography, it may be possible to view differences in the white matter tracts connecting V1 and extrastriate PPC. If the high-level motion system in strabismic amblyopia is functional, one should see prominent connections between V1 and extrastriate motion areas. However, because water diffusion is bidirectional along the path of the tract, it would not be possible using DTI alone to differentiate the direction in which the tracts project. Whether the connections are biased towards bottom-up (low-level) or top-down (high-level) cortical processing can not be determined. Other tools such as magnetoencephalography (MEG) which

provides excellent temporal resolution would need to be utilized to make further conclusions regarding the temporal properties of the neural activity.

MEG is a non-invasive technique which assesses neural activity by recording magnetic field changes believed to correlate with electrophysiological activity of summated post-synaptic potentials (Hämäiläinen, Hari, Ilmoniemi, Knuutila & Lounasmaa, 1993). The magnetic evoked responses are detected with a magnetometer positioned around the subject's head, in a location that would be optimal for data collection from a specific brain region. Latency and power (amplitude) of the evoked potentials in response to presentation of a visual stimulus can then be analyzed and compared across individual subjects. In a study using MEG, responses recorded from occipital cortex of strabismic participants with amblyopia showed longer latencies and reduced power when stimuli were viewed with the amblyopic eye relative to the fellow eye (Anderson, Holliday & Harding, 1999). More recently, Anderson and Swettenham (2006) presented data recorded from a strabismic individual with amblyopia using a MEG analysis technique called synthetic aperture magnetometry. With this technique, magnetic field activity is recorded using a whole-head imaging system. The output for a particular brain region is determined using the weighted sum of a specific combination of MEG sensors within the sensor array that is located inside the MEG helmet. Detection of neural activity for a specific brain region is done using the unique weighted sum within the sensor array that corresponds to that particular brain area. In that study, MEG data were co-registered to MRI data using specialized software to form functional brain images. The authors concluded that extrastriate deficits in global form processing exist and attributed their findings to asynchrony in neuronal firing patterns. MEG reflects synchronous neural activity in the population of cells within the brain region being recorded. This MEG evidence provides support for the proposed theory that asynchronous neural activity is part of the cortical deficit in strabismic amblyopia (Roelfsema, Konig, Engel, Sireteanu & Singer, 1994). From the presented fMRI data, cortical activity in V1 and in extrastriate areas appeared to be dysfunctional in amblyopia relative to controls. By conducting studies where the fMRI results are combined with MEG data (which has high temporal resolution), it may become possible to distinguish dysfunction in top-down processes from bottom-up processes based on the locations and latency of magnetic field signals evoked in response to high-level and low-level RDK stimuli.

### *6.3 Clinical implications*

Current clinical assessments do not evaluate motion perception. The findings from the experiments presented here suggest that deficits in low-level and high-level motion processing are associated with anisometropic and strabismic amblyopia. Furthermore, these deficits may be related to binocular function which is generally dysfunctional in amblyopia to some extent. Although not directly tested in these experiments, of particular importance may be the possible relationship between motion deficits and stereopsis of a coarser scale (Dmax for disparity detection). Our findings are in line with several others suggesting that binocularity may be of significance in predicting psychophysical deficits in form (McKee, Levi & Movshon, 2003) and motion (Ho et al., 2005, McColl & Mitchell, 1998, Reed & Burdett, 2002) perception. Unfortunately, the outcome of occlusion therapy is not always predictable and sometimes unsuccessful in achieving the desired level of improvement in visual acuity. The degree to which binocular function or motion processing is impaired could be an indicator of treatment failure (or success). These measures may play an important role in the diagnosis of amblyopia and, in the long term, may guide future research to determine the benefits of remediation for these visual losses in amblyopia.

There have been a growing number of studies suggesting that the visual system maintains some neural plasticity into adulthood (reviewed in Levi, 2006). Several studies have looked at the benefits of occlusion therapy and vision training in adults. Occlusion therapy has been shown to be effective in improving aspects of spatial vision such as visual acuity (Wick, Wingard, Cotter & Scheiman, 1992) and positional acuity (Simmers & Gray, 1999). Vision training has also been shown to improve performance on visual tasks of vernier acuity (Levi & Polat, 1996; Levi, Polat & Hu, 1997), positional acuity (Li & Levi, 2004), letter identification (Levi, 2005) and contrast sensitivity (Polat et al., 2004) most likely through perceptual learning mechanisms. Polat and colleagues suggest that training with a specific task may not be limited to improved performance on that task only but may also positively influence performance in other aspects of visual performance. It has not yet been determined whether aspects of motion perception may also improve with training and practice. It may also be possible to view these neural changes using DTI techniques because changes in white matter have been

shown to be possible with repeated practice of a specific task (Bengtsson, Nagy, Skare, Forsman, Forssberg & Ullen, 2005).

It is possible that complete visual deprivation of the fellow eye induced by occlusion therapy may contribute to motion perception deficits. The extent of occlusion (i.e. time that the fellow eye is visually deprived) varies depending on the VA loss in the amblyopic eye at the time of diagnosis, and the effectiveness of occlusion therapy. A mildly amblyopic eye measured at the time of the study could belong to a child with severe amblyopia and successful results from aggressive occlusion therapy or to a child with mild amblyopia who received minimal occlusion therapy. Because of this variability, visual acuity in the amblyopic eye, after occlusion therapy has been completed, may not be a good predictor for the extent of deficits in the fellow eye.

Contrary to this, it is also possible that motion deficits may improve, parallel to VA, during occlusion therapy. Leguire et al. (1990) determined that contrast sensitivity losses in the fellow eye improved with occlusion therapy alongside VA and contrast sensitivity improvements in the amblyopic eye of children. This suggests that through binocular integration, occlusion therapy that takes place during the critical period and aims to improve visual deficits in the amblyopic eye may also result in improvements in the fellow eye.

Improvement on a specific visual task is possible only if occlusion therapy begins during the critical period for that task (Daw, 1998). It is feasible that motion deficits that are mediated by highly binocular cortical areas could improve with occlusion therapy provided that treatment is timed appropriately. Developmental differences between M/dorsal pathway and P/ventral pathway tasks exist (Atkinson, 1992). Performance on motion tasks reaches adult levels earlier than form tasks (Parrish et al., 2004). Because of these developmental differences, one can not assume that the critical period during which improvement may be possible on specific motion tasks is simultaneous with the critical period during which improvement is seen for VA. Longitudinal studies assessing low-level and high-level motion perception in amblyopic and fellow eyes concurrently with VA at the onset of, during, and after occlusion therapy would provide insight into developmental differences in the neural pathways for motion and form perception.

Furthermore, and most importantly, it may help to provide a clearer understanding regarding the clinical impact and relevance of having neural deficits in these visual processing pathways.

## 6.4 References


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**APPENDIX:** **University of British Columbia Research Ethics Board Certificates of Approval for psychophysical and fMRI studies pertaining to this thesis**

The University of British Columbia
Office of Research Services and Administration
**Behavioural Research Ethics Board**

## *Certificate of Approval*

| PRINCIPAL INVESTIGATOR | DEPARTMENT | NUMBER |
|---|---|---|
| Giaschi, D.E. | Ophthalmology & Visual Science | B01-0499 |

INSTITUTION(S) WHERE RESEARCH WILL BE CARRIED OUT
Children's & Women's Health Centre ,

CO-INVESTIGATORS:
Ho, Cindy, Ophthalmology & Visual Science; Parrish, Emillie, Psychology; Zwicker, Amy, Psychology

SPONSORING AGENCIES:
Natural Science Engineering Research Council

TITLE:
Brain Mechanisms Underlying Human Motion Perception

| APPROVAL DATE (yr/mo/day) | TERM (YEARS) | AMENDMENT | AMENDMENT APPROVED |
|---|---|---|---|
| 03-10-30 | 1 | Oct. 2003, Consent forms | JAN 16 2004 |

CERTIFICATION:

The protocol describing the above-named project has been reviewed by the Committee and the experimental procedures were found to be acceptable on ethical grounds for research involving human subjects.

*Approval of the Behavioural Research Ethics Board by one of the following:*
Dr. James Frankish, Chair,
Dr. Cay Holbrook, Associate Chair,
Dr. Susan Rowley, Associate Chair

This Certificate of Approval is valid for the above term provided there is no change in the experimental procedures

The University of British Columbia
Office of Research Services,
Clinical Research Ethics Board – Room 210, 828 West 10th Avenue, Vancouver, BC V5Z 1L8

# *Certificate of Full Board Approval*

***Clinical Research Ethics Board Official Notification***

| PRINCIPAL INVESTIGATOR | DEPARTMENT | NUMBER |
|---|---|---|
| Giaschi, D.E. | Ophthalmology & Visual Science | **C04-0071** |

INSTITUTION(S) WHERE RESEARCH WILL BE CARRIED OUT
Children's & Women's Health Centre

CO-INVESTIGATORS:
Ho, Cindy, Ophthalmology & Visual Science

SPONSORING AGENCIES
Canadian Institutes of Health Research

TITLE :
Low- and High-Level Motion Processing in Children with Anisometropic or Strabismic Amblyopia

| APPROVAL DATE | TERM (YEARS) | DOCUMENTS INCLUDED IN THIS APPROVAL: |
|---|---|---|
| Mar 31 2004 | 1 | Protocol; Advertisement dated February 2004; Letter of Initial Contact dated February 2004; Parental consent form (control S:1, 2b, 3a; 3b; 3c; S4) dated February 2004; Parental consent form (subject S:1; S2b S:4) dated February 2004; Child assent form (S:1; S2b; 3a; 3b; 3c) dated February 2004 |

CERTIFICATION:
**In respect of clinical trials:**
*1. The membership of this Research Ethics Board complies with the membership requirements for Research Ethics Boards defined in Division 5 of the Food and Drug Regulations.*
*2. The Research Ethics Board carries out its functions in a manner consistent with Good Clinical Practices.*
*3. This Research Ethics Board has reviewed and approved the clinical trial protocol and informed consent form for the trial which is to be conducted by the qualified investigator named above at the specified clinical trial site. This approval and the views of the this Research Ethics Board have been documented in writing.*

The documentation included for the above-named project has been reviewed by the UBC CREB, and the research study, as presented in the documentation, was found to be acceptable on ethical grounds for research involving human subjects and was approved by the UBC CREB.

**The CREB approval for this study expires one year from the approval date.**

*Approval of the Clinical Research Ethics Board by one of:*
Dr. P. Loewen, Chair
Dr. A. Gagnon, Associate Chair
Dr. J. McCormack, Associate Chair

The University of British Columbia
Office of Research Services and Administration
**Behavioural Research Ethics Board**

# *Certificate of Approval*

| PRINCIPAL INVESTIGATOR | DEPARTMENT | NUMBER |
|---|---|---|
| Giaschi, D.E. | Ophthalmology & Visual Science | B01-0499 |

INSTITUTION(S) WHERE RESEARCH WILL BE CARRIED OUT
Children's & Women's Health Centre ,

CO-INVESTIGATORS
Ho, Cindy, Ophthalmology & Visual Science; Zwicker, Amy, Psychology

SPONSORING AGENCIES
Natural Science Engineering Research Council

TITLE
Brain Mechanisms Underlying Human Motion Perception

| APPROVAL RENEWED DATE | TERM (YEARS) | AMENDMENT | AMENDMENT APPROVED |
|---|---|---|---|
| NOV - 4 2004 | 1 | Oct. 25, 2004, Co-Investigator | NOV - 4 2004 |

CERTIFICATION:

The protocol describing the above-named project has been reviewed by the Committee and the experimental procedures were found to be acceptable on ethical grounds for research involving human subjects.

*Approval of the Behavioural Research Ethics Board by one of the following:*
Dr. James Frankish, Chair,
Dr. Cay Holbrook, Associate Chair,
Dr. Susan Rowley, Associate Chair
Dr. Anita Hubley, Associate Chair

This Certificate of Approval is valid for the above term provided there is no change in the experimental procedures

The University of British Columbia
Office of Research Services,
Clinical Research Ethics Board – Room 210, 828 West 10th Avenue, Vancouver, BC V5Z 1L8

# *Certificate of Expedited Approval: Renewal*

***Clinical Research Ethics Board Official Notification***

| PRINCIPAL INVESTIGATOR | DEPARTMENT | NUMBER |
|---|---|---|
| Giaschi, D.E. | Ophthalmology & Visual Science | **C04-0071** |

INSTITUTION(S) WHERE RESEARCH WILL BE CARRIED OUT

Children's & Women's Health Centre

CO-INVESTIGATORS:

Ho, Cindy, Ophthalmology & Visual Science

SPONSORING AGENCIES

BC Ministry of Children and Family Development

TITLE :

Low-level and High-level Motion Processing in Amblyopic Children

| APPROVAL RENEWAL DATE | TERM (YEARS) | AMENDMENT: | AMENDMENT APPROVED: |
|---|---|---|---|
| 8 March 2005 | 1 | | |

CERTIFICATION:

**In respect of clinical trials:**

*1. The membership of this Research Ethics Board complies with the membership requirements for Research Ethics Boards defined in Division 5 of the Food and Drug Regulations.*

*2. The Research Ethics Board carries out its functions in a manner consistent with Good Clinical Practices.*

*3. This Research Ethics Board has reviewed and approved the clinical trial protocol and informed consent form for the trial which is to be conducted by the qualified investigator named above at the specified clinical trial site. This approval and the views of this Research Ethics Board have been documented in writing.*

The Chair of the UBC Clinical Research Ethics Board has reviewed the documentation for the above named project. The research study, as presented in the documentation, was found to be acceptable on ethical grounds for research involving human subjects and was approved for renewal by the UBC Clinical Research Ethics Board.

**The CREB approval for renewal of this study expires one year from the date of renewal.**

*Approval of the Clinical Research Ethics Board by one of:*
Dr. James McCormack, Interim Chair
Dr. Alain Gagnon, Associate Chair

The University of British Columbia
Office of Research Services and Administration
**Behavioural Research Ethics Board**

# *Certificate of Approval*

| PRINCIPAL INVESTIGATOR | DEPARTMENT | NUMBER |
|---|---|---|
| Giaschi, D.E. | Ophthalmology & Visual Science | **B01-0499** |

INSTITUTION(S) WHERE RESEARCH WILL BE CARRIED OUT:
Children's & Women's Health Centre ,

CO-INVESTIGATORS:
Ho, Cindy, Ophthalmology & Visual Science

SPONSORING AGENCIES:
Natural Science Engineering Research Council

TITLE:
Brain Mechanisms Underlying Human Motion Perception

| APPROVAL RENEWED DATE | TERM (YEARS) | AMENDMENT | AMENDMENT APPROVED |
|---|---|---|---|
| OCT 19 2005 | 1 | Oct. 5, 2005, Co-PI / Consent form | OCT 19 2005 |

CERTIFICATION:

The protocol describing the above-named project has been reviewed by the Committee and the experimental procedures were found to be acceptable on ethical grounds for research involving human subjects.

*Approval of the Behavioural Research Ethics Board by one of the following:*
Dr. Peter Suedfeld, Chair,
Dr. Susan Rowley, Associate Chair

This Certificate of Approval is valid for the above term provided there is no change in the experimental procedures

The University of British Columbia
Office of Research Services,
Clinical Research Ethics Board – Room 210, 828 West 10th Avenue, Vancouver, BC V5Z 1L8

# *Certificate of Expedited Approval: Amendment*

***Clinical Research Ethics Board Official Notification***

| PRINCIPAL INVESTIGATOR | DEPARTMENT | NUMBER |
|---|---|---|
| Giaschi, D.E. | | **C04-0071** |

INSTITUTION(S) WHERE RESEARCH WILL BE CARRIED OUT

Children's & Women's Health Centre

CO-INVESTIGATORS:

Ho, Cindy, Ophthalmology & Visual Science

SPONSORING AGENCIES

BC Ministry of Children and Family Development

TITLE :

Low-level and High-level Motion Processing in Amblyopic Children

| APPROVAL DATE (yy/mm/dd) | TERM (YEARS) | AMENDMENT: | AMENDMENT APPROVED: |
|---|---|---|---|
| 06-03-10 | 1 | Parental Subject Consent Form (S: 2a) Version dd March 2006; Parental Control Consent Form (S: 2a) Version dd March 2006 | **11 April 2006** |

CERTIFICATION:

**In respect of clinical trials:**

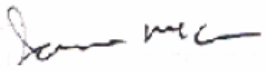
*1. The membership of this Research Ethics Board complies with the membership requirements for Research Ethics Boards defined in Division 5 of the Food and Drug Regulations.*

*2. The Research Ethics Board carries out its functions in a manner consistent with Good Clinical Practices.*

*3. This Research Ethics Board has reviewed and approved the clinical trial protocol and informed consent form for the trial which is to be conducted by the qualified investigator named above at the specified clinical trial site. This approval and the views of this Research Ethics Board have been documented in writing.*

The amendment(s) for the above-named project has been reviewed by the Chair of the University of British Columbia Clinical Research Ethics Board and the accompanying documentation was found to be acceptable on ethical grounds for research involving human subjects.

**The CREB approval period for this amendment expires on the one year anniversary date of the CREB approval for the entire study.**



*Approval of the Clinical Research Ethics Board by one of:*
Dr. Gail Bellward, Chair
Dr. James McCormack, Associate Chair