Extrastriate form and motion processing in cone dysfunction and normal vision

Eliza A. Burton

Department of Visual Neuroscience

UCL Institute of Ophthalmology

Thesis submitted for the degree of Doctor of Philosophy

2016

Declaration Statement

I, Eliza Burton, confirm that the work presented in this thesis is my own. Where information has been derived from other sources, I confirm that this has been indicated in the thesis.

Abstract

Cone disorders result in poor visual acuity and colour blindness. While previous studies have investigated low-level vision, little is known about how cone loss impacts on extrastriate vision. This thesis used behavioural psychophysics and steady-state VEP (SSVEP) to examine effects of cone loss on coherent form, coherent motion and biological motion perception. Chapter one introduces the topic and background literature. Chapter two outlines the methods used within this thesis. Chapter three investigates the impact of simulated low-vision on form and motion perception. Normally sighted participants completed behavioural and SSVEP tests under blurred conditions. Blur led to reductions in perceptual sensitivity and coherence-related cortical signals in all three tasks, with coherent form perception faring the worst. Chapter four describes collection of control data for subsequent comparison with patient groups: behavioural and SSVEP measures under differing light levels chosen to stimulate rods and/or cones. The fifth and sixth chapters examine extrastriate vision in patients with stationary and progressive cone disorders. Comparisons of patients and controls on scotopic performance, mediated by rods reveal the extent to which cortical visual processing may have developed atypically in this group. Behavioural results in chapter 5 show that even at scotopic levels, cone disorder patients show some perceptual and SSVEP impairments compared to controls. Progressive patients show scotopic impairments on all three tests while stationary patients have impairments on coherent form and motion but not biological motion tests. Scotopic contrast sensitivity was also measured to check if extrastriate deficits could be explained by low-level deficits. Chapter six examines SSVEP results in the stationary patient group. Patients showed reduced VEP amplitudes relative to controls and there was some evidence of atypical motion topography. Results suggest that atypical photoreceptor function can affect the development and function of extrastriate vision. Potential advances in treatments for genetic visual disorders raise questions regarding neural plasticity, including the extent to which cortical visual processing can be reorganised following restoration of photoreceptor function.

Acknowledgements

First and foremost I would like to thank my supervisors Dr Marko Nardini, Prof. Gary Rubin and the late Dr John Wattam-Bell. They provided me with knowledge, enthusiasm and inspiration throughout my PhD. I would also like to thank Prof. Janette Atkinson and Prof. Oliver Braddick who gave tireless support and advice throughout.

This work would not have been possible without the clinicians involved in this project, Dr Michel Michaelides and Dr Jonathan Aboshiha. Alongside them my gratitude goes to the patients and controls who volunteered their time to take part in this research.

I have to thank my fellow lab members Fleur Corbett, Tessa Dekker, Sara Garcia, Pete Jones, Sarah Kalwarowsky, Louisa Kulke, Aisha McLean, Karin Petrini and Alicia Remark for providing not only academic support but friendship and fun as well.

Finally, I would like to thank my family; my parents, my husband Ross and my daughter Corinne for giving me reason to smile when things got tough.

Funding

This PhD was funded by the UCL Graduate School and the Special Trustees of Moorfields Eye Hospital and the NIHR Biomedical Research Centre at Moorfields Eye Hospital NHS Foundation Trust through a UCL Grand Challenge Grant.

CONTENTS

LIST OF PUBLICATIONS

Data included in the following chapters have been submitted for publication:

Chapter 3: Burton, E., Wattam-Bell, J., Rubin, G. S., Atkinson, J., Braddick, O., & Nardini, M. (2015). The effect of blur on cortical responses to global form and motion. *Journal of Vision, 15(15),* 1-14.

Chapter 4: Burton, E., Wattam-Bell, J., Rubin, G. S., Atkinson, J., Braddick, O., & Nardini, M. (2015). Cortical processing of global form, motion and biological motion under low light levels. *Journal of Vision, 121(2016),* 39-49.

Chapter 5: Burton, E., Wattam-Bell, J., Rubin, G. S., Aboshiha, J., Michaelides, M., Atkinson, J., Braddick, O., & Nardini, M. (In press). Dissociations in coherence sensitivity reveal atypical development of cortical visual processing in patients with congenital achromatopsia. *IOVS*.

LIST OF ABBREVIATIONS

2AFC	-	Two-alternative forced choice
ACHM	-	Achromatopsia
AULCSF	-	Area Under the Log Contrast Sensitivity Function
BOLD	-	Blood-Oxygen-Level Dependent
Cd/m^2	-	Candela per Square Meter
CPD	-	Cycles per Degree
CS	-	Contrast Sensitivity
CSF	-	Contrast Sensitivity Function
EEG	-	Electroencephalogram
FFA	-	Fusiform Face Area
fMRI	-	Functional Magnetic Resonance Imaging
LGN	-	Lateral Geniculate Nucleus
LogST	-	Log Scotopic Trolands
LogWC	-	Log Weber contrast
MT	-	Middle Temporal Area
MST	-	Medial Superior Temporal Area
PCD	-	Progressive Cone Dystrophy
PLD	-	Point-Light Display
pSTS	-	Posterior Superior Temporal Sulcus
RDK	-	Random Dot Kinematogram
SF	-	Spatial Frequency
SSVEP	-	Steady-State Visual Evoked Potential
TE	-	Inferotemporal Cortex area
TEO	-	Temporo-Occipital area
VEP	-	Visual Evoked Potential

LIST OF FIGURES

LIST OF TABLES

Chapter 1. INTRODUCTION

1.1 GENERAL INTRODUCTION

The human visual system can demonstrate a remarkable degree of plasticity, adapting and changing throughout life to new visual experiences. Questions about plasticity in humans have been explored through studies of visual deprivation, for example in patients with sight loss. Through studying cases of visual deprivation, it is possible to explore the manner in which visual brain development depends on experience, what happens to the visual brain when vision is lost, and also in some cases when vision is restored. New therapies such as gene replacement therapy and stem cell therapy are now offering the possibility of sight restoration in those with retinal disease, in particular genetic disorders of photoreceptor function. The ability of the visual system as a whole to make use of any new signals provided by the retina will be key to the success of such new therapies. A thorough understanding of the effects of photoreceptor dysfunction on multiple aspects of visual perception is therefore an important complement to new therapies being trialled now and in the near future.

The aim of this thesis was to explore a subset of cortical visual functions, not previously investigated, in patients with cone dysfunction. Three visual skills were studied – perception of coherent form, coherent motion and biological motion. By studying visual sensitivity in normally sighted controls and patients with cone disorders it was possible for the first time to gain insight into the effects of rod-only vision on mid- and high-level vision.

This thesis contains 7 chapters, with a brief summary of the contents of each chapter below:

Chapter 1 introduces the aims of this research and describes the relevant literature in a series of reviews. This begins with a review of the literature on cortical vision before focussing on the effects of visual deprivation, in particular on extrastriate vision. Details are then given on the rod and cone systems and scotopic perception. The final literature review covers the cone disorders studied within this thesis.

Chapter 2 details the methodologies used within this thesis. These include (a) behavioural tests of extrastriate visual function – specifically, detection of global form, global motion and biological motion, (b) behavioural tests of basic visual function – specifically, contrast sensitivity, and (c) electroencephalography (EEG) measures of global form and motion processing.

Chapter 3 explores the impact of simulated low vision on global form, global motion and biological motion perception in participants with healthy vision. By filtering out high spatial frequencies from coherent form and motion stimuli using a diffuser screen, we were able to simulate acuity and contrast sensitivity loss such as that experienced by many clinical populations, including cone disorder patients. Participants completed behavioural psychophysics and EEG (Steady-state VEP; SSVEP) testing.

Chapter 4 describes the collection of a control dataset. Normally sighted participants completed global form, global motion and biological motion perception behavioural psychophysics and SSVEP. This was done under four light conditions ranging from photopic to scotopic. The aim of testing under different light conditions was to study vision under solely rod and cone conditions as well as under combinations of the two. The dataset allows for subsequent comparison with cone disorder patients. Controls under scotopic conditions are in theory matched to cone disorder patients, in the sense that both groups must rely only on their rods for vision. Deviations from controls in the scotopic

condition could therefore represent changes in perception due to atypical visual development, and/or impairments to rod function in the patient groups.

Chapter 5 details the collection of behavioural data with patients with stationary and progressive cone disorders. These patients underwent the same behavioural test procedure as controls. Comparison between these patients and controls allows us to see the impact of long-term rod-only vision on mid- and high-level visual perception.

Chapter 6 describes EEG results for the patients introduced in chapter 5. Patients completed EEG tests of global form and motion processing under varying light conditions. This allowed the neural effects of cone disorders on extrastriate vision to be examined.

Chapter 7 gives a summary of the results from each chapter before going on to discuss general conclusions which can be drawn from across chapters, including limitations and future directions.

1.2 LITERATURE REVIEW: CORTICAL VISION

The visual pathways projecting from the eye to the visual cortex as well as pathways within the visual cortex itself have been studied extensively. These have allowed understanding of both the segregation and integration of visual information as it travels from the eye throughout the brain.

Visual signals, initially captured within the retina and relayed via subcortical processes, arrive at the striate cortex, containing visual area V1. From here further aspects of visual processing are mediated by extrastriate cortex, including areas V2, V3, V4 and V5/MT. Functionally the striate and extrastriate can be described as processing low-level and mid/high-level vision respectively. This is a consequence of the hierarchical structure of the visual system, in which 'lower-level' aspects of cortical vision such as grating acuity and contrast sensitivity depend most on initial processing within the striate cortex, while mid/high-level vision, for example, coherent form and motion perception and biological motion perception, are processed by the extrastriate brain regions.

1.2.1 Early Visual Pathways

Hubel & Livingstone (1987) proposed a tripartite model of the visual system in which different categories of visual information were conveyed along three separate neural pathways. Information from magnocellular, parvocellular and magno-parvo-pathways were believed to project in parallel from the lateral geniculate nucleus (LGN) to the primary visual cortex. Functional segregation was then believed to be maintained as they fed into area V2. While this early model provides a useful schematic of the early visual system, more recent evidence, has shown that the three pathways show considerable interaction, both feed-forward and feed-back, throughout the visual system (e.g. Sincich & Horton, 2005).

Within the LGN there are six layers, or laminae. Of these, the first two receive magnocellular input while laminae 3-6 receive parvocellular input. Konio cells which were discovered later than both magno and parvo cells due to their small size, reside in-between the laminae. The magnocellular and parvocellular pathways remain segregated as they travel from the LGN to V1; however it is in V1 that the first evidence of cross-talk between these two pathways becomes apparent (Sincich & Horton, 2005).

V1 consists of 6 cortical layers arranged dorsally to laterally. Layer 1 consists almost entirely of dendritic and axonal connections. Layers 2/3 (known as the supragranular layer) receives input from all pathways of the LGN and contains feed-forward projections to areas including V2, V3, V4 and MT. There appears to be considerable interaction between different types of visual information conveyed within layers 2/3 (Sincich & Horton, 2005). However, it is also true that some of the signals continue to maintain their strict segregation within V1, for example projections to MT are known to come almost entirely from the magnocellular pathway. Layer 4 of V1, known as the granular layer, is made up of four sublayers – 4A, 4B, 4Ca and 4Cb. The magnocellular and parvocellular projections from the LGN feed into sublayers 4Ca and 4Cb respectively. Layers 5/6 of V1 (the infragranular layers) provide feedback to the LGN (Purpura et al., 1988).

Originally Hubel and Livingstone proposed that V1 was functionally organised based on its layers and distinctive structural areas known as patches and interpatches, which appear when V1 is stained with cytochrome oxidase (Hubel & Livingstone, 1987). Colour was proposed to be processed by the patch cells of layer 2/3 while orientation was thought to be processed by interpatch cells of layer 2/3. Motion was thought to be processed by layer 4B as these cells were found to be colour non-specific but direction and orientation specific. This has since been supported by more recent studies investigating the projections within the visual cortex. It is known for example that the magnocellular pathways project from the LGN to layer 4B and then onto V2 and MT (Sincich & Horton, 2005).

While V1 has patch and interpatch areas, V2 presents with a distinctive striped pattern when stained, with stripes appearing perpendicular to V1. These stripes appear thick, thin or pale. V1 patches feed into the thin stripes while interpatches feed into the pale stripes. Layer 4B of V1 (conveying motion information) appears to feed exclusively into the thick layers of V2. The thin and pale stripes then project on to V4 while the thick stripes project to MT (Sincich & Horton, 2005). These pathways can be seen in Figure 1.1.

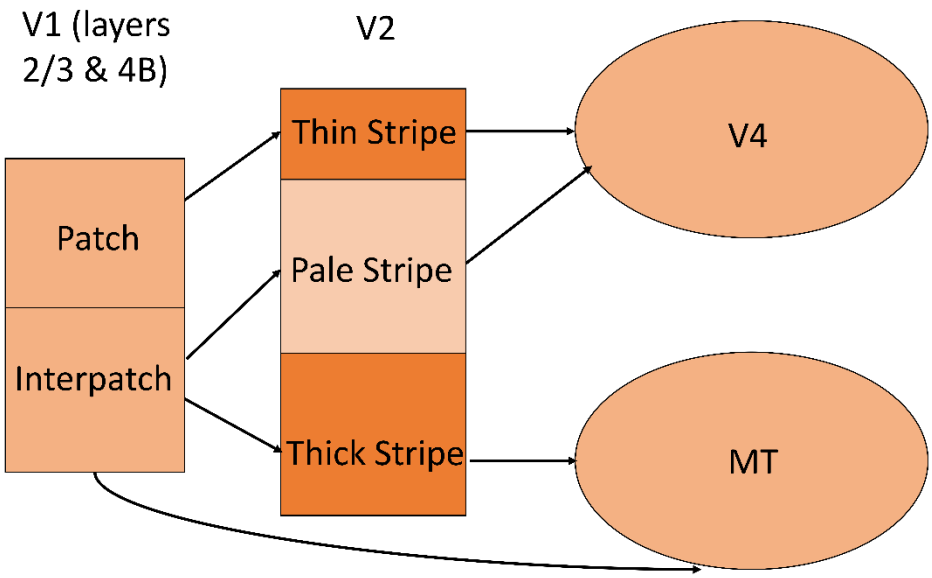

Figure 1.1. Schematic of V1, V2 visual pathways feeding into V4 and MT.

The pathways described here can also be described functionally. The magno-V1-V2-MT pathway, known as the dorsal pathway, conveys information on spatial localisation and motion integration. The parvo-V1-V2-V4 pathway, known as the ventral stream, carries information about colour and form and is important for object recognition (Goodale & Milner, 1992; Mishkin, Ungerleider, & Macko, 1983)

1.2.2 High-Level (Extrastriate) Vision

As mentioned previously the hierarchical structure of the visual system results in progressively more complex aspects of vision being processed further along extrastriate cortex. As visual information is processed within extrastriate cortex, higher areas have larger receptive fields and can be understood as integrating more and more lower-level "features" to make increasingly more complex discriminations.

Higher-level vision covers many different kinds of perceptual abilities varying in complexity. At one end there are 'mid-level' processes integrating low-level visual information such as those involved in coherent form and motion perception, while at the other end are highly specialised skills such as recognition of complex forms including faces or scenes, and use of vision to guide movements.

Some of the most complex aspects of visual recognition have been mapped to specific brain regions within the temporal lobe. The fusiform face area, for example, is believed to be involved in face perception (Grill-Spector, Knouf, & Kanwisher, 2004; Kanwisher, McDermott, & Chun, 1997; Kanwisher & Yovel, 2006; Kanwisher, 2000; Tong, Nakayama, Moscovitch, Weinrib, & Kanwisher, 2000) although the extent to which this region is specialised for faces or simply responsive to complex visual information remains under debate (Gauthier, Tarr, Anderson, Skudlarski, & Gore, 1999; Xu, 2005).

Within this thesis, three types of higher-level vision are focussed on – global form, global motion and biological motion. Global form and motion were chosen due to their importance in forming the groundwork for later higher-level perception, their relative input from the dorsal vs. the ventral visual pathways and their extensive use in studies of typical and atypical development. Biological motion perception was chosen as a higher-level skill believed to receive input from both dorsal and ventral pathways.

1.2.2.1 Coherent (Global) Form Perception

The ability to perceive visual form is mediated by structures within the ventral stream of the cortical visual system. In order to perceive form the visual system must integrate disparate local signals into a global construct.

The earliest model of form perception postulated that visual information travelled along a strict hierarchical ventral pathway through V1-V2-V4-TEO-TE (Mishkin et al., 1983; Mishkin & Ungerleider, 1982). However, it is now known that alongside the main ventral pathway there are multiple additional pathways and interactions involved. Information can bypass the main central stream and reach TEO through MT via MST, FST, V4s and TEOd. These additional connections help explain why lesions in macaques to the central ventral stream do not always result in a reduction in firing rate in V4 or TEO neurons (Kravitz, Saleem, Baker, Ungerleider, & Mishkin, 2013). Alternative pathways can allow some low-level visual information to reach higher levels of cortex even when much of the ventral stream is disabled.

The perception of form includes a range of visual processes ranging from initial recognition of basic shapes, through to complex object recognition. The hierarchical nature of the visual system is well demonstrated by form perception. Local visual elements are first processed by primary visual cortex, which has small receptive fields, but many such elements seem eventually to be combined into representations of more complex shapes or objects by temporal cortex neurons (Haxby et al., 2001; Kobatake & Tanaka, 1994; Riesenhuber & Poggio, 1999). Situated as an intermediary between these is coherent form perception. Coherent form perception involves integrating low-level visual cues into a global structure through the combination of local orientation and higher-order features.

V1 neurons have small receptive fields which are able to detect local form cues. These are then sent via V2 and V3 to V4 where they are combined. Ostwald, Lam, Li, & Kourtzi (2008) carried out an fMRI study of BOLD responses to viewing concentric, radial and translational global form stimuli. They reported that while early-visual areas respond to local stimulus cues, only higher-visual regions respond to the global structure of the form. They were able to examine the pathways involved in global form perception using multivariate analysis models and identified early visual signals processed in V1 as being relayed to higher ventrolateral occipital regions. Braddick, O'Brien, Wattam-Bell, Atkinson, & Turner (2000) also demonstrated the importance of extrastriate regions in the processing of coherent form. They found activation in the middle occipital gyrus, ventral occipital surface and intraparietal sulcus in response to coherent form stimuli. These were distinct from extrastriate regions activated by coherent motion although there was no distinction between the two in activation at V1.

Coherent form perception is often studied using glass patterns. Elements (dots or short line segments) are aligned to create the impression of a form. Local information over small regions remains the same making these stimuli good for teasing apart global from local processing. The percentage of signal to noise elements can be varied to change the coherence level. This tests the limits of the visual system's ability to integrate the local cues. By testing participants at a range of coherence levels, their coherence threshold can be calculated.

1.2.2.2 Development of Coherent (Global) Form Perception

The development of coherent form perception is dependent on post-natal experience, with infants first displaying preference of coherent form at 12 weeks (Atkinson et al., 2004). Psychophysical thresholds then improve throughout infancy and childhood until as late as 14 years of age (e.g. Kovács, Kozma, Fehér, & Benedek, 1999), although by around 8

years of age form coherence sensitivity is close to adult values in many studies (e.g. Atkinson and Braddick, 2005). Changes have also been observed in brain regions associated with higher-level object recognition (FFA and STS) which continue to increase in size throughout childhood, up to 16 years of age (Golarai et al., 2007). This suggests that development of coherent form perception is ongoing throughout childhood. Disruption during this time, for example through visual deprivation, may therefore lead to problems with coherent form perception. A detailed examination of this is given in a later section of this literature review ('Visual Deprivation').

1.2.2.3 Coherent (Global) Motion Perception

Much like coherent form perception, coherent motion perception describes a mid-level visual skill in which early-level information is integrated to allow for more complex percepts. For example motion signals from our surroundings are integrated to create the impression of optic flow – the flow of motion created by the changing position of the eye relative to the visual scene. This is important for balance and navigation in the environment as well as perception of moving objects in our surroundings (Gibson & Gibson, 1957; Gibson, 1954).

Coherent motion perception is mediated by area MT/V5 and V3/V3a within the visual cortex (Braddick et al., 2001,Watson et al., 1993). MT is important for the integration of local motion signals into a single coherent motion. Coherent motion is processed via the dorsal stream which runs from V1 to parietal regions (Kravitz, Saleem, Baker, & Mishkin, 2011). Information can arrive at MT/V5 from a number of sources. This can be direct from V1 or from other visual regions including V2 and V3 (Felleman & Van Essen, 1991). Parietal regions, receiving input from MT are able to further process the information for example parietal region MST is important for detecting optic flow (Duffy & Wurtz, 1991, 1995; Morrone et al., 2000; Orban et al., 1992).

Coherent motion thresholds can be measured in a similar way to coherent form. **Error! Reference source not found.** can also demonstrate an example of a coherent motion stimulus, in which each line segment would represent the trajectory of a single moving dot. This would create rotational motion containing a percentage of randomly oriented, noise dots. Other types of coherent motion can also be created by changing the global organisation of the dots, so that the motion is for example translational, expanding, contracting or radiating.

1.2.2.4 Development of Coherent Motion Perception

Much like form perception, coherent motion perception has a long developmental trajectory and is dependent on post-natal development. From VEP studies infants have been shown to display sensitivity to the direction of global motion between 6 and 8 weeks (Wattam-Bell, 1996). In comparison of sensitivity to global motion and global form infants showed a VEP response to switches between 100% coherence and 0% coherence at an earlier age for motion than for form (Wattam-Bell et al., 2010). The age at which motion coherence thresholds match those of adults has been disputed. Adult-levels have been reported in 6 year olds (Ellemberg, Lewis, Maurer, Brar, & Brent, 2002) but other studies have not found this until 10 or 11 years of age (Atkinson & Braddick, 2005; Braddick, Atkinson, & Wattam-Bell, 2003; Gunn et al., 2002; Spencer et al., 2000). Hadad et al (2011) found coherent motion thresholds only became adult-like at age 14 years, later than previous studies had suggested. The conclusion from these studies is that the type of stimuli, speed of motion, dot density and whether the temporal parameters allow individual dots to be tracked, are all likely to lead to variations in results between different studies. However, in developmental disorders, a general finding is that across many different genetic and acquired disorders motion coherence sensitivity is poor relative to form coherence sensitivity (Braddick et al., 2003).

In order to establish differences in the development of coherent form and motion perception it is important to have comparable stimuli. Many studies deal with form or motion sensitivity in isolation (Atkinson et al., 2004; Braddick et al., 2003; Gunn et al., 2002; Janine Spencer et al., 2000), however this limits the conclusions that can be drawn regarding differences in the developmental trajectories of form and motion. Using stimuli matched in their configuration allows for comparison between form and motion performance. Such stimuli were first described by Atkinson and Braddick (2005) and have been applied to developmental populations (Atkinson & Braddick, 2005; Wattam-Bell et al., 2010).

1.2.2.5 Biological Motion Perception

Biological motion refers to the pattern of movement generated by the locomotion of a living organism. Perception of biological motion is an essential skill for social communication as well as for recognising living creatures in the environment. Biological motion presents a particularly interesting type of motion perception as it has been argued to involve the spatiotemporal integration of form and motion cues, requiring not only perception of the motion of the dots but extraction of the overall structure as well. Studying biological motion perception may therefore allow for the study of integration between ventral and dorsal stream signals.

Johansson (1973) demonstrated that biological motion can be detected when motion is reduced down to a few points of light representing the joint positions of a human or animal. These type of stimuli have been termed point-light displays (PLDs) and have been used extensively to study biological motion perception (E.g. Bardi, Regolin, & Simion, 2011; Paviova, Krägeloh-Mann, Sokolov, & Birbaumer, 2001; Ayse Pinar Saygin, Wilson, Hagler Jr, Bates, & Sereno, 2004; Simion, Regolin, & Bulf, 2008; Vanrie & Verfaillie, 2004). Figure 1.2 illustrates an example of a PLD. PLDs create a stimulus which can only be understood when in motion. When stationary the displays tend to present a

disorganised array of dots, however the introduction of motion immediately creates the perception of a figure in motion. This stripping back of extraneous visual cues in PLDs allows the study of spatiotemporal dynamics of biological motion perception.

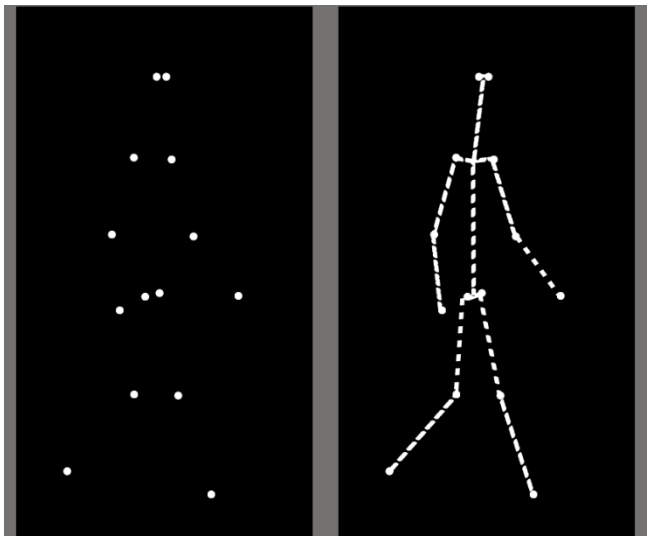

Figure 1.2. Example of a point light display representing a walking figure. The dotted lines have been added to the figure on the right to demonstrate the shape of the figure but stimuli only consist of the white dots shown on the left.

The posterior superior temporal sulcus (pSTS) has been identified as a key region for the detection of biological motion in neuroimaging studies (Grossman & Blake, 2002; Grossman et al., 2000; Puce & Perrett, 2003, 2003; Saygin, 2007). The pSTS receives input from both of the dorsal (via MST) and the ventral (via TE) pathways providing motion and form information (Grossman et al., 2000; Oram & Perrett, 1994). The integration of these allows biological motion to be perceived. Other brain regions which have been implicated in the perception of biological motion include the cerebellum (Grossman et al., 2000), occipital and fusiform face area (Grossman & Blake, 2002) and premotor areas (Saygin, 2007).

The role of form perception in biological motion has been debated. It has been argued that the sparse information presented in each frame of a PLD is integrated across time to give

the impression of a figure (Beintema & Lappe, 2002; Lange, 2006; Pinto & Shiffrar, 1999). This fits with a computational model of biological motion perception (Giese & Poggio, 2003) which proposes that form and motion are both important elements for the integration of biological motion within neural structures such as the pSTS.

However, there is evidence questioning the importance of form perception in the recognition of biological motion. This comes from studies of patients with lesions to ventral regions of the visual cortex (Gilaie-Dotan, Bentin, Harel, Rees, & Saygin, 2011; Sharon Gilaie-Dotan, Saygin, Lorenzi, Rees, & Behrmann, 2015). Although these patients had very limited form perception, their ability to recognise biological motion (free of noise) was unimpaired. This suggests that biological motion perception is possible, in some circumstances, without the ventral stream. The relative roles of ventral and dorsal pathways in the perception of biological motion therefore remain unclear and open to further investigation.

1.2.2.6 Development of Biological Motion Perception

Similar to global form and motion perception, biological motion is known to have a long developmental trajectory (Hadad, Maurer, & Lewis, 2011). While new-born infants have been found to show sensitivity to biological motion in preferential looking experiments (Bardi et al., 2011; Bertenthal, Proffitt, & Cutting, 1984; Simion et al., 2008) the ability to recognise biological motion does not reach adult levels until 4-5 years (Pavlova, Krägeloh-Mann, Sokolov, & Birbaumer, 2001; Sweeny, Wurnitsch, Gopnik, & Whitney, 2013; Zhao et al., 2014) with this increasing to 11 years if the motion is displayed in noise (Freire, Lewis, Maurer, & Blake, 2006; Hadad et al., 2011; Simion et al., 2008). Hadad et al (2011) compared the development of biological motion (in noise) and coherent motion perception using stimuli matched for speed and found similar rates of development.

1.2.3 Conclusion

Coherent form, coherent motion and biological motion represent some of the many types of visual processing carried out within the extrastriate cortex. Through these three types of perception it is possible to understand the contribution of both the dorsal and ventral pathways to vision, as well as the integration of these in the case of biological motion. The long developmental trajectories of form, motion and biological motion perception suggest that visual experience may be important. Studies with populations with visual deprivation reviewed next provide direct evidence for this.

1.3 LITERATURE REVIEW: VISUAL DEPRIVATION

Much of what is known about the plasticity of the visual system comes from studies of visual deprivation. During development the visual cortex demonstrates experience-dependent plasticity, adapting its structure and activity patterns based on visual input. However, periods of developmental plasticity can be limited and long-term impairments may result if the brain is deprived of visual input during early sensitive or "critical" periods. The time-course, duration and recovery period of deprivation can all impact on visual development and these can differ depending on the visual function being considered. Previous findings on visual deprivation and plasticity have the potential to shed light on the prospect of sight-restoring therapies.

1.3.1 Low-Level vision and striate cortex

1.3.1.1 Animal Models

Early work into visual deprivation was predominantly carried out using animal models and focussed on the striate cortex.

Hubel and Wiesel conducted some of the most significant work into visual deprivation through their work on cats and monkeys. By suturing eyelids at different points during post-natal development Hubel and Wiesel explored the impact on the visual cortex using single neurone recordings (Hubel, Wiesel, & LeVay, 1976, 1977; Hubel & Wiesel, 1970; Wiesel & Hubel, 1974). One of their key findings was that there was a sensitive period for visual development, during which time as little as 3 days' visual deprivation in kittens, was enough to reduce the number of cells in the LGN and parts of the visual cortex which would usually respond to the deprived eye (Hubel & Wiesel, 1970). This is in contrast to cats deprived during adulthood who showed no change in sensitivity after a year of deprivation suggesting that plasticity of V1 reduces rapidly after the first year.

Hubel and Wiesel also found that recovery after deprivation was severely limited. Visual deprivation between 10-51 days of life resulted in a loss of neuronal responses to the deprived eye which still persisted a year after de-suturing, (Hubel & Wiesel, 1970). This indicates a short period of sensitivity for development of ocular dominance in V1 after which time there is insufficient plasticity to correct an imbalance in the dominance of V1 neurons.

While the effects of deprivation within the sensitive period appear long-term, these effects can be lessened if vision is restored early enough. Blakemore & Sluyters (1974) found that opening the deprived eye and suturing the other eye, during the sensitive period, led to reversals in ocular dominance but the degree of change was directly related to when reverse suturing occurred. Movshon & Blakemore (1974) built on this work, carrying out a number of reverse suturing experiments. They reported that after 4 weeks deprivation in kittens who had one eye sutured since eye opening, de-suturing led to a complete reversal of ocular dominance within a week, however, after 5 weeks deprivation this effect was halved. These results show that the effects of deprivation can be reversed but that timing is important.

Subsequent work built on early findings by exploring other aspects of vision such as motion detection and binocularity. The effects of motion deprivation have been tested by rearing cats under stroboscopic illumination in which a flashing light allows some vision but prevents any experience of motion (Cynader, Berman, & Hein, 1973; Pasternak, Merigan, & Movshon, 1981). Electrophysiological results show reductions in neural responses to motion and binocularity following stroboscopic rearing (Cynader et al., 1973; Orban, Kennedy, Maes, & Amblard, 1978). This indicates that typical motion experience is necessary for the development of both normal motion sensitivity and binocularity.

Behavioural studies have also shown long-term deficits in spatial acuity in motion-deprived cats (Pasternak et al., 1981). Pasternak et al (1981) found directional sensitivity improved if previously deprived cats went on to receive extensive training (viewing of

moving gratings), however spatial acuity remained poor. This suggests a sensitive period for spatial acuity within the first 12 months but potential for a longer sensitive period for motion sensitivity if given intensive exposure following deprivation.

The impact of selective motion deprivation has also been explored. By placing kittens within a rotating drum their visual experience can be confined to unidirectional gratings (Daw & Wyatt, 1976). This has shown that the development of motion direction sensitivity is experience dependent. Neuronal recordings taken from the kittens demonstrated normal directional sensitivity for the motion they were exposed to but reduced sensitivity to other directions. Similar results have been reported in orientation sensitivity (Blakemore & Cooper, 1970; Hirsch & Spinelli, 1970). Cats reared in an environment made up of vertical orientations who an increase in neuronal firing to vertical and decrease to horizontal stripes. The opposite is true of cats reared in horizontal striped environments (Blakemore & Cooper, 1970; Hirsch & Spinelli, 1970).

Motion sensitivity appears to have a short sensitive period after which time plasticity becomes limited. Motion deprived kittens exposed to only leftwards or rightwards motion, followed by a reversal after 5 weeks, continued to show a cortical preference to the direction they were first exposed to. In contrast to this, kittens who are monocularly deprived for the first 5 weeks, followed by a reversal in their deprivation to the other eye show a cortical preference to the eye that was opened last (Berman & Daw, 1977) indicating a longer period of sensitivity.

1.3.1.2 Human Research

Animal models have provided crucial information about critical periods of visual development. Studies with humans show the extent to which similar processes affect visual development in young patients with atypical visual experience. Much of the research into human visual deprivation has been gathered from patients with amblyopia.

Amblyopia – loss of visual function with a cortical basis, i.e. with no defect at the level of

the eye – can be caused by a range of conditions including strabismus, congenital cataracts, ptosis or anisometropia. The standard treatment is patching of the dominant eye to allow vision from the amblyopic eye to improve. While this leads to improvements in spatial acuity it can also lead to a loss of binocularity.

Treatment for amblyopia is rarely attempted after 10 years of age due to the belief that the benefits would be limited because of a lack of plasticity in the visual system (Astle, McGraw, & Webb, 2011; Holmes et al., 2011; Hussein, Coats, Muthialu, Cohen, & Paysse, 2004). For example, while some studies suggest improvement to spatial acuity can be achieved after the age of 10 years these improvements are limited compared to those seen at younger ages (Astle et al., 2011; Hertle et al., 2007; Oliver, Neumann, Chaimovitch, Gotesman, & Shimshoni, 1986). Some treatments aimed at strengthening binocular vision however have been shown to be effective into adulthood (Hess, Mansouri, & Thompson, 2010; Wick, Wingard, Cotter, & Scheiman, 1992). This research suggests that the sensitive period for spatial acuity in humans comes before 10 years of age while binocular vision has a more prolonged developmental trajectory.

Both monocular and binocular deprivation have been studied in patients with deprivational amblyopia resulting from congenital cataracts. Congenital cataracts can affect one or both eyes and are usually surgically removed within the first year of life. Both acuity and contrast sensitivity in those who previously had congenital cataracts is worse following unilateral rather than bilateral deprivation (Birch, Stager, Leffler, & Weakley, 1998; Birch & Stager, 1988; Lewis, Maurer, & Brent, 1995). However, this is dependent on the age at which cataracts are removed. Early treatment of unilateral cataracts (before 8 weeks of age) has been found to lead to acuity and contrast sensitivity outcomes matched to those treated for bilateral cataracts (Birch et al., 1998) suggesting that prior to 8 weeks the visual system is able to adapt to input from the treated eye but after 8 weeks this becomes more difficult and competition between the two eyes is established.

Patients whose cataracts remain untreated throughout childhood experience long-term monocular or binocular deprivation. This is the case for many children seen by project Prakash, a joint humanitarian, and scientific project aimed at providing sight restoring treatment to socially deprived populations in India. Acuity was assessed in 53 children who were treated for bilateral congenital cataracts between the ages of 8 to 18 years (Ganesh et al., 2014). The majority showed significant improvements in visual acuity 6 months after treatment, with 61% being able to read, with glasses post-treatment. No differences in acuity were identified based on age. This suggests that improvements to visual acuity can be made after long-term deprivation spanning several years. Similar results were found for contrast sensitivity (Kalia et al., 2014) with children aged 8-17 years exhibiting improvements in contrast sensitivity post-treatment.

1.3.1.3 Conclusion: Low-Level Vision

Work on low-level vision has established that there are sensitive periods for visual development. The exact nature of the sensitive period is dependent on the particular aspect of vision being examined. For example, ocular dominance columns appear to show very little change in activation after their sensitive period has ended (Hubel & Wiesel, 1970), however abilities such as motion sensitivity and binocularity can be developed after their initial sensitive period given the right exposure and training (Hess et al., 2010; Pasternak et al., 1981; Wick et al., 1992).

1.3.2 High-level (Extrastriate) Vision

The impact of visual deprivation on higher-level vision has been explored by examining human populations who have undergone atypical visual development due to visual deprivation, such as those with amblyopia discussed previously. Studies have tended to focus on specific aspects of visual perception. Here I will focus on those covered in this thesis; coherent form, coherent motion and biological motion perception.

1.3.2.1 Coherent Form Perception

Coherent form perception is impaired in children who have been treated for bilateral congenital cataracts (Lewis et al., 2002). Lewis et al (2009) measured form coherence thresholds in children who had received treatment for congenital cataracts within the first year of life. Participants were presented with a two-alternative forced-choice (2AFC) test in which they had to identify a circular form, similar to those shown in **Error! Reference source not found.**. On average, bilateral cataract participants' coherence thresholds were 1.6 times worse than controls. Those with unilateral cataracts, however, showed normal form perception. This suggests that input from one eye is sufficient for the development of coherent form perception. This contrasts with the effects seen on acuity, suggesting that there are cooperative rather than competitive effects between the eyes at this level of processing.

Project Prakash has carried out a case study of a patient known as SRD who was born with congenital cataracts, which were removed only at the age of 12 years. The research team examined SRD twenty years after she had her cataracts removed (Ostrovsky, Andalman, & Sinha, 2006). Unlike the cataract patients studied by Lewis et al (2002), SRD was not tested on coherent form perception but rather on general object recognition such as shape matching at which she performed within the normal range, although it took her slightly longer to select a correct response. It remains possible that problems may have become apparent if coherence tests were used. SRD may also have had some vision during childhood which could have maintained the visual pathways required for the development and maintenance of form perception. Alternatively it could be that SRD's visual system was sufficiently plastic to allow her to develop new visual skills following on from her period of deprivation.

A further study carried out as part of Project Prakash examined recently treated cataract patients' ability to match their new visual experience with touch (Held, Ostrovsky, & Sinha,

2008). Participants were presented with objects either visually or haptically and then asked to identify the object when presented either visually or haptically, a second time alongside a distractor. Participants were at chance level for matching touch and vision immediately following vision restoration but as little as 5 day after treatment participants began to develop the ability to match visual and haptic stimuli. This study suggests that while patients can recognise objects soon after treatment, matching this with other senses takes longer.

1.3.2.2 Coherent Motion Perception

Coherent motion thresholds in children treated for bilateral cataracts are around 5 times worse than controls of the same age (compared to 1.6 times worse in those with unilateral cataracts) (Ellemberg et al., 2002). This contrasts with acuity and contrast sensitivity which are both more severely affected by unilateral as opposed to bilateral cataracts. The importance of patterned visual input for the development of coherent motion along with the binocularity of area MT is thought to be responsible for this discrepancy (Ellemberg et al., 2002). Patterned input from one eye in the case of unilateral cataracts is believed to be sufficient to drive the development of coherent motion perception in extrastriate regions.

Motion thresholds in cataract patients are relatively higher than form thresholds suggesting an increased vulnerability to visual deprivation. This is in line with theories of dorsal stream vulnerability in which visual functions mediated by the dorsal stream are more vulnerable to developmental delay than those mediated by the ventral stream. This has been shown in a range of visual and developmental disorders (Atkinson & Braddick, 2007, 2011; Atkinson et al., 1997; Braddick, Atkinson, & Wattam-Bell, 2003; Gunn et al., 2002; Spencer et al., 2000; Taylor, Jakobson, Maurer, & Lewis, 2009).

Comparison of coherent motion perception in children with congenital and developmental bilateral cataracts suggests that the sensitive period for development of coherent motion

perception may be short. Ellemberg et al (2002) found that children who had been diagnosed with bilateral cataracts between 8 and 57 months, with no prior history of ocular abnormality, and underwent deprivation for 1-6 months before treatment did not show any deficit on motion coherence tasks. This is in contrast to infants with congenital cataracts who went through a similar duration of deprivation and showed marked impairments in coherent motion perception. This suggests that patterned visual input in the first 8 months of life is necessary for normal development of coherent motion perception and that short term deprivation (of 1-6 months) following this does not impact on coherent motion perception.

Other studies of long-term deprivation have found motion perception to be relatively spared compared to form and object recognition. MM and SB both lost their vision during childhood but had it restored many years later due to corneal grafts. Both patients struggled with recognising objects and faces but reported movement as being easy to detect (Fine et al., 2003; Gregory, 2003). The patients were not tested specifically on coherent motion tasks as the cataract patients were, so it is possible that on more specific tests, they may have shown impairments. It may be the case that the early vision these two experienced before their sight loss was enough to drive the development of motion perception to a sufficient level, allowing it to be maintained throughout the period of vision loss. Another potential explanation is that the two patients still had some experience of motion as their vision loss was not absolute and they could both detect light and dark. This crude visual input may have been sufficient to allow moving stimuli to be detected which in turn could have maintained the functionality of the motion pathways within the brain.

1.3.2.3 Biological Motion Perception

Studies of children with congenital cataracts have found biological motion is relatively spared compared to global form and motion perception (Hadad, Maurer, & Lewis, 2012;

Lewis, Hadad, & Maurer, 2010). Patients showed impairments of global motion perception at both 4 degrees/second and 18 degrees/second. However the same participants showed no impairments at biological motion perception using stimuli matched in speed to the global motion stimuli (Lewis et al., 2010). Similar results have been observed in patients with amblyopia, with patients demonstrating normal biological motion perception despite associated deficits in early-level vision (Neri, Luu, & Levi, 2007; Thompson, Troje, Hansen, & Hess, 2008).

Biological motion perception is believed to be processed within the pSTS, a convergence point for the dorsal and ventral streams (Grossman et al., 2000; Puce & Perrett, 2003). However, the sparing of biological motion perception compared to coherent form and motion perception suggests that additional pathways outside of the traditional ventral/dorsal routes may contribute to its perception. This appears to be specific to the biological nature of the stimuli as perception of non-biological motion defined form has been found to be impaired in patients with amblyopia (Giaschi, Regan, Kraft, & Hong, 1992; Hayward, Truong, Partanen, & Giaschi, 2011)

“Mirror neurons” have been proposed as one such alternative system via which biological motion perception develops (Hadad et al., 2012). Mirror neurons are specialised cells, identified in monkeys, which respond to both the performance and passive viewing of an action, and are proposed to provide a substrate for some kinds of social interaction. They are only activated by species-specific actions and have been proposed in humans (based on fMRI results), primates and some birds (Rizzolatti & Craighero, 2004; Rizzolatti, Fadiga, Fogassi, & Gallese, 1999). It may be that these kinds of additional neural pathways help bolster the visual signal allowing the detection of biological motion when visual input is reduced.

1.3.3 Evidence of Cortical Reorganisation Following Deprivation

The potential reorganization of the visual cortex following sight loss may be one way in which vision is optimised when input signal is reduced. Changes in response to altered experience (e.g. ocular dominance changes in the initial studies by Hubel and Wiesel) can be understood as a flexible deployment of limited neural resources to best represent the sensory signal that is available. Animal models have also demonstrated the potential of the visual cortex to reorganise following retinal lesions (Chino, Kaas, Smith, Langston, & Cheng, 1992; Darian-Smith & Gilbert, 1995; Eysel et al., 1999; Kaas et al., 1990; Schmid, Rosa, & Calford, 1995). However, there is a lack of consensus on the degree to which reorganisation can occur and one fMRI study has found no evidence of reorganisation in macaque V1 following retinal lesions (Smirnakis et al., 2005).

In humans, the effects of deprivation and the possibilities for reorganisation have been studied using fMRI. Work has been carried out with patients who have developed scotomas, (Baker, Dilks, Peli, & Kanwisher, 2008; Baseler et al., 2011; Baseler, Gouws, & Morland, 2009; Cornelissen, Haak, & Morland, 2013; Morland, 2011), as well as patients born with a central scotoma as seen in congenital achromatopsia (Baseler et al., 2002).

Baker, Peli, Knouf, & Kanwisher (2005) studied fMRI responses in area V1 of patients with complete loss of central vision due to macular degeneration. They found peripheral stimuli were able to generate activation in regions of V1 which were usually only responsive to central vision. In a follow-up study patients with complete verses partial central vision loss were compared (Baker et al., 2008). Only patients with a total absence of central vision (within the fovea) showed remapping. This effect was true regardless of the age of the patient or how long they had had macular degeneration. From this the authors concluded that residual central vision prohibits reorganisation from taking place and total loss of central vision is key.

However, Baseler et al. (2011) found no evidence of reorganization in 16 adults with juvenile and age-related forms of macular degeneration. They found no difference in fMRI signal at the lesion projection zone in patients with macular degeneration and those with simulated central scotomas. These patients all demonstrated complete absence of foveal vision. The authors suggested that V1 responses seen in the scotoma zone of patients, seen in previous studies, could be the result of greater feedback from extrastriate cortex rather than remapping within area V1.

As well as those with acquired vision loss, individuals with congenital vision loss have been studied. Visual plasticity is known to reduce with age and so may be more evident in those born with a visual condition compared to those who develop one later in life. Baseler et al., (2002) studied retinotopic organisation in V1 in three patients with congenital achromatopsia. These patients all demonstrated a central scotoma that had been present from infancy. Surprisingly, given an absence of functional cones, the area of V1 that usually represents the cone-rich foveola was found to be active in the patients with congenital achromatopsia. Given the absence of functioning cones in these patients, the authors concluded that experience-dependent reorganisation had occurred within V1. There may be fewer obstacles to such reorganisation in a patient group with congenital vision loss, such as congenital achromatopsia, than in patients who experience progressive changes to their vision starting later in life.

1.3.4 Conclusion

How human visual processing develops following a period of vision loss is determined by a number of factors including the type of deprivation, when in life it occurs and the duration of vision loss. All these factors can make it hard to predict the consequences of sight restoration. Evidence of cortical reorganisation in those with late onset vision loss is mixed, while reorganisation has been demonstrated in patients with congenital vision loss. The potential for reorganisation following new therapies therefore remains unclear.

Establishing a baseline of visual function in patients prior to any new therapies is a crucial first step in understanding how the brain reacts to visual deprivation.

1.4 LITERATURE REVIEW: THE ROD AND CONE SYSTEMS

The human visual system is capable of processing information across a large range of light intensities, in excess of 10 log units (Hood & Finkelstein, 1986). This is made possible by the shift from cone to rod vision allowing maximum photon capture in low light conditions through spatial and temporal summation.

Cones are active in bright light and allow us to perceive with high spatial resolution. The three different classes of cone cell (S, M and L) detect different wavelengths of light allowing the perception of colour. The high resolution and colour sensitivity of cone cells allows sharp vision in bright light, however they become ineffective in low light. Rod photoreceptors, on the other hand, are highly sensitive to light and as a result they enable our scotopic vision. Rod photoreceptors are found extra-foveally and in greater numbers than cones in the human eye, with over 100 million compared to ~6 million cones (Chen & Sampath, 2013).

Rod vision has low spatial and temporal resolution, compared to the cones. Spatial resolution of the rods is limited by their convergence onto ganglion cells. Within the fovea, cones converge onto ganglion cells with a ratio of 1:1 allowing high resolution information to be conveyed through the retina. Rods on the other hand have a convergence ratio of ~20:1 (Chen & Sampath, 2013). Rods are therefore connected in such a way as to produce large areas of spatial summation while cones can achieve both large and small spatial summation (Hess, Sharpe, & Nordby, 1990). Cones within the fovea also have the advantage of the greatest photoreceptor density anywhere in the retina, optimising this region for high spatial acuity (Purves et al., 2001). Outside of the fovea rods are more densely represented than cones but their high convergence ratio with ganglion cells continues to limit their spatial resolution.

Reduced temporal perception under scotopic vision is due to longer temporal integration in the rods, with rods requiring up to 100ms to integrate the visual input compared to 10-15ms in cones (Boothe, 2006). This longer integration allows increased sensitivity in low light but comes at the cost of reduced temporal resolution. Temporal integration is related to temporal summation in which individual quanta of light are summed over time by the eye. This follows Bloch's Law of temporal summation expressed as:

$$R = I.T$$

R = response, I = intensity and T = time.

Threshold value (R) is therefore a product of luminance intensity (I) and stimulus duration (T). In low light in which luminance intensity is reduced, stimulus duration needs to be longer in order for threshold to be reached. This holds up to durations of around 100ms (Boothe, 2006).

Rods and cones convey information through the retina along distinct pathways before converging along post-retinal networks.

Information is transmitted from photoreceptors to ganglion cells via bipolar cells. Rods transfer information to rod-specific bipolar cells in the outer plexiform layer, with each single bipolar cell receiving information from 15-30 rods (Kaufman, Alm, & Adler, 2003). From here rod bipolar cells convey their information to amacrine cells. These are important for boosting the signal power of rods as they summate multiple rod signals (Kaufman et al., 2003). There are two main classes of amacrine cell which receive information from rods – the A11 cells and the A17 cells (Kaufman et al., 2003). A11 cells play an important role in connecting rods and cones via gap junctions which allows fast transmission of the rod signal.

The rod system has at least two methods of transmission through the retina - the slow and fast pathways. The slow pathway is active in low mesopic and scotopic conditions and

involves the transmission of information from the rods to the ganglion cells via rod bipolar and A11 amacrine cells. The fast pathway, active under mesopic conditions, involves transmission via rod-cone gap junctions. This allows rods to synapse onto cone bipolar and ganglion cells, and therefore allowing faster transmission of information. Cone photoreceptors have a faster rate of conduction than rod photoreceptors due to a more direct pathway through the retina. Cones synapse onto cone bipolar cells which then synapse directly onto retinal ganglion cells, without the need for intermediate amacrine cells (Kaufman et al., 2003).

1.4.1 Scotopic Vision

1.4.1.1 Low-Level Vision

Low-level scotopic vision has been widely researched covering areas such as local motion detection, acuity, stereopsis, flicker fusion and spectral sensitivity (e.g. Barlow, 1962; Cavonius & Robbins, 1973; Gegenfurtner, Mayser, & Sharpe, 2000; Kellnhofer, Ritschel, Vangorp, Myszkowski, & Seidel, 2014; Kinney, 1958; Livingstone & Hubel, 1994; Mandelbaum & Sloan, 1947; Nygaard & Frumkes, 1985; Riggs, 1965; Teller, 2009; Westheimer, 1965).

Van Nes, Koenderink, Nas, & Bouman (1967) carried out a number of experiments detailing the effects of luminance on spatial vision. They recorded contrast sensitivity functions under different luminance levels. They showed that as luminance decreases and vision shifts from cone-mediated to rod-mediated, the CSF shifts from band-pass to low-pass in shape. The cut-off spatial frequency of the CSF which represents the maximum acuity possible in any given light condition, also showed a sharp reduction as luminance fell. Cut-off spatial frequency was 55 cpd at 5900 photopic trolands but reduced to just 5 cpd at 0.09 photopic trolands. Reductions in both spatial acuity and contrast sensitivity in low light can be explained by increased spatial integration of the rod system.

Motion detection under scotopic conditions has been investigated by Gegenfurtner et al. (2000). They investigated the effects of scotopic luminance on direction and velocity discrimination of sinusoidal gratings. Direction discrimination was unaffected by reductions in luminance, however, velocity discrimination was reduced by around 20% in scotopic compared to photopic conditions for temporal frequencies below 4 Hz. They attributed this to greater temporal averaging within the rod system, reducing the contribution to velocity perception of motion detectors tuned to higher temporal frequencies. Takeuchi & De Valois (2000) also found that velocity judgements of drifting sinewave gratings were impaired in low light with velocity sensitivity peaking at 3 Hz. They ascribed this to low-pass temporal filtering of the rod system, leading to reduced temporal perception of high velocity stimuli. Impairments in low-level motion perception therefore appear to be velocity dependent.

1.4.1.2 High-Level (Extrastriate) Vision

Determining the exact input from rods vs cones into extrastriate visual processing is far from straightforward due to the complex neural pathways feeding into this system. Studying extrastriate vision under scotopic conditions allows the opportunity to understand more about how rods and cones contribute differentially to extrastriate function.

Previous research into extrastriate vision under scotopic conditions has tended to focus on higher-level motion processing. While it is apparent that motion processing is possible under scotopic light, the impact of associated reductions in spatial and temporal resolution are less clear. Area MT/V5 of the occipital lobe, has been shown to be an important area in the perception of motion (Cook & Maunsell, 2002; Martinez-Trujillo, Cheyne, Gaetz, Simine, & Tsotsos, 2007; Newsome & Pare, 1988). MT is known to receive a majority magnocellular input (Maunsell, Nealey, & DePriest, 1990) which in turn is where the majority of rods input to (Chen & Sampath, 2013; Lee, Smith, Pokorny, & Kremers, 1997; Sun, Pokorny, & Smith, 2001). This suggests that under scotopic conditions, the

magnocellular pathway receives more input from rods than the parvocellular pathway and this may help preserve motion perception in low light.

The idea that coherent motion perception is preserved in low light is supported but only under certain conditions, namely when the motion velocity is slow. This is in keeping with the findings of Takeuchi & De Valois (2000). For example, Billino, Bremmer, & Gegenfurtner (2008), found coherence detection thresholds became progressively worse as light levels fell from 98.5 to 0.285 and 0.018 cd/m^2, if velocity exceeded 6.6 deg/sec. Grossman & Blake (1999) did not find coherence thresholds significantly reduced under low light, however their study only tested up to 8.8 deg/sec which may not have been fast enough to see disruption of motion processing. The reason why high velocities can disrupt coherent motion perception is believed to be due to the sluggishness of the rod system, rendering it unable to process rapidly moving stimuli.

Biological motion perception was also investigated in the two studies mentioned above. Biological motion requires the precise extraction and integration of temporal and spatial cues in order for the motion to be detected. Given the fact that coherent motion is disrupted at high velocity in scotopic conditions it would be likely that a similar result would be found for biological motion.

Billino et al (2008) asked participants to detect biological motion as opposed to phase-scrambled motion under the three light conditions mentioned previously. They found a U-shaped result with performance worst at mid-light levels (0.285 cd/m^2), improving in scotopic conditions. The extraction of structure in biological motion is reliant on temporal dynamics and Billino et al argued that a disruption of this could explain why biological motion is relatively impaired under mesopic conditions. They point to the role of conflicting information carried by fast and slow rod pathways through the retina, as a possible explanation for the disruption under mesopic conditions.

Under some mesopic conditions both fast and slow rod pathways are likely to be active. This can cause rod-cone cancellation, first demonstrated by Macleod (MacLeod, 1972), in which flicker detection is cancelled out by opposing rod and cone signals at mesopic levels when frequencies reach close to 15 Hz. This occurs due to the slow and fast retinal pathways cancelling each other out. This results in asynchronous information reaching the visual cortex which in turn disrupts the spatio-temporal processing required for biological motion perception.

Grossman & Blake (1999) found that biological motion detection became worse in low light. However they only tested under two light conditions, 3.6 and 0.036 cd/m^2. It may be that had they tested under lower light conditions they would have found performance began to improve again as was the case for Billino et al (2008).

Other types of complex motion investigated include radial flow and form-from motion (Billino et al., 2008; Grossman & Blake, 1999). These have both been found to be impaired under scotopic conditions, believed to be due to the reduced spatial and temporal resolution of the rod system.

Coherent form perception has not been studied under scotopic conditions and so the relative contribution of the rod system remains unknown. Perception of coherent form is thought to be dominated by the parvocellular system (Wilkinson et al., 2000; Wilson, Wilkinson, & Asaad, 1997; Wilson & Wilkinson, 1998) which in turn receives the majority of its input from cone pathways. This would predict that coherent form perception would show substantial impairments under scotopic conditions.

The studies described all attempted to isolate rod vision by testing typical participants in scotopic conditions. However, this only provides an indication of scotopic vision. It is not possible to determine in these studies exactly when cones became inactive and as a result it is not possible ascribe the results in low light solely to the rod system. Another issue with using scotopic vision as a model of rod-only vision is that it involves testing of

rods in suboptimum conditions. Rods are known to see best in mesopic conditions (Hess et al., 1990). However, due to the contribution of cones at this light level, in healthy sighted individuals, rod vision is usually studied at much lower light levels. Rods are therefore underperforming in these conditions and results from these studies provide an underestimation of what rods alone can achieve.

One way that rod vision can be isolated is to study individuals who have no active cones due to eye disease. Cone disorders can therefore provide a useful insight into rod vision - although differences in these patients' rod-based visual abilities could in principle also reflect atypical development of visual processing.

1.5 LITERATURE REVIEW: INHERITED CONE DISORDERS

1.5.1 Introduction

Inherited cone disorders consist of a range of retinal conditions characterised by absence or damage to the cone photoreceptors. Due to the heterogeneous nature of these disorders, symptoms vary with genotype and to some degree from individual to individual.

In this section I will outline the cone disorders dealt with in this thesis. These cover both a stationary cone disorder (congenital achromatopsia), present from birth, and progressive cone dystrophies which present in late childhood or early adulthood.

1.5.2 Cone Disorders as a Model for Rod Vision

The cone disorders provide a rare opportunity to gain a greater understanding of rod vision. Issues surrounding testing of normally sighted individuals under scotopic conditions such as the possible influence of cones, and the suboptimal testing of rods under scotopic conditions can also be overcome.

In order to probe rod vision for a range of stimuli and across different light conditions, a person must ideally have no cone activity. Patients with cone disorders can therefore offer insights into how rod vision functions.

1.5.3 Congenital Achromatopsia

Congenital Achromatopsia (ACHM), also known as rod monochromacy, is a hereditary condition affecting ~1 in 30 000 people (Aboshiha, Dubis, Carroll, Hardcastle, & Michaelides, 2015; Johnson et al., 2004). It is characterised by a lack of functioning cone photoreceptors and is present from birth. The main symptoms include reduced visual acuity, photophobia and colour blindness. Patients also exhibit a central scotoma and eccentric fixation.

1.5.3.1 Clinical Features

ACHM can be classified as complete and incomplete depending on the degree of cone dysfunction. Patients tested within this thesis had complete achromatopsia in which there is no discernible cone function. Complete achromatopsia is usually apparent by 6 months of age at which time an infant may exhibit photophobia and nystagmus (Remmer, Rastogi, Ranka, & Ceisler, 2015). Nystagmus tends to reduce with age to the point where it may be absent in adulthood.

ACHM leads to reduced visual acuity which is typically 20/200-20/400 in adults (Nishiguchi, Sandberg, Gorji, Berson, & Dryja, 2005). Some patients have had their acuities recorded as high as 20/25-20/40 however this is thought to represent acuity in incomplete achromatopsia (Nishiguchi et al., 2005). Acuity in ACHM can be significantly affected by the amount of light in the environment. Patients' acuity typically peaks in the high scotopic/mesopic light range at which the rod signal peaks (Johnson et al., 2004).

Photophobia is another clinical manifestation of ACHM due to the fact that bright light bleaches patients' rods and leaves them without vision. Characteristic squinting and blinking are seen in patients in an attempt to reduce the amount of light entering the eye. In recent years, dark glasses and contact lenses have been developed to aid vision in daylight.

Full-field ERG responses are often normal in congenital achromatopsia due to normal functioning rod photoreceptors. Multi-focal ERG however typically shows reduced or absent ERG response at 30 or 15 Hz in cone driven pathways (Remmer et al., 2015).

1.5.3.2 Genetics

ACHM is an autosomal recessive condition. Transmission is autosomal recessive and six genes have been identified; *GNAT2*, *PDE6C*, *PDE6H*, *ATF6*, *CNGA3* and *CNGB3* which together account for approximately 70-80% of all cases (Aboshiha et al., 2015; Remmer et al., 2015). Of these, ~70% of cases are caused by mutations in either *CNGA3* or *CNGB3* (Komáromy et al., 2010). All except *ATF6* encode components of the cone-specific phototransduction cascade and disruption to this is therefore believed to underlie the cone dysfunction. Whether ACHM is complete or incomplete is not related to a specific genotype and different degrees of achromatopsia as well as progressive cone dystrophies appear to be caused by the same mutation in different family members. For example, Wissinger et al. (2001) studied 258 patients with *CNGA3* mutations and found a combination of complete and incomplete achromatopsia as well as patients with progressive cone disorders. Differences within the same genotype are believed to be due to specific differences in the type of mutation. Rosenberg et al. (2004) showed how two family members with different types of mutation in the *GNAT2* gene (a frameshift mutation and a splicing defect) had different variations of achromatopsia. One exhibited incomplete achromatopsia while the other had preserved colour perception.

1.5.3.3 Histology

It was originally postulated that ACHM was the result of a complete lack of cone photoreceptors (Galezowski, 1868), however later histological evidence clearly showed there were cones present in the eyes of ACHM patients (Glickstein & Heath, 1975). Reports differ on whether these cones are normally distributed and formed, however most agree that they are not present in the fovea and show a variety of abnormalities (Glickstein & Heath, 1975). One reason for the variation in results is likely due to retinal changes associated with age. Although ACHM is classed as a stationary disorder, evidence has also shown that while cones may not be functioning, they do show progressive degeneration with age (Thiadens et al., 2010). However, the exact impact this may have on vision, if any, is little understood. Lee et al. (2015) recently examined the retinae of 10 children aged 2.4 – 98. 7 months, using optical coherence tomography, to address how the retina develops in achromatopsia. They found signs of typical development in the children with achromatopsia, such as increases in retinal thickness with age, however changes were delayed and reduced compared to controls. Their results suggest that the retinal structure in achromatopsia is not stationary from birth and continues to develop throughout childhood, however how this might affect visual function remains unclear.

Recent studies have found little evidence of age-associated changes in vision or retinal thickness in patients ranging in age from 6-52 years (Aboshiha, Dubis, et al., 2014; Sundaram et al., 2014). Aboshiha et al (2014) carried out a longitudinal study examining 38 patients at baseline and at 12-24 month follow-ups. They found no evidence of changes in retinal structure or visual functioning over this time and no link between age or genotype and disease progression. Sundaram et al (2014) also reported no significant correlation between patient age and retinal thickness despite patients ranging from 6-52 years of age. These results support the view of achromatopsia being a stationary disorder.

1.5.3.4 Contrast Sensitivity and Visual Acuity

Contrast sensitivity in ACHM has been shown in some cases to be comparable to healthy sighted controls in scotopic ranges and peaks within the mesopic range (Hess & Nordby, 1986). Hess & Nordby, (1986) reported on one patient with normal scotopic sensitivity. While contrast sensitivity was comparable to a control when luminance was below 180 scotopic trolands (STr) (~ 9 cd/m^2)[1] once above this contrast sensitivity fell until completely absent at 1800 STr (~ 91 cd/m^2)[1]. This can be explained by the fact that the rod cells become bleached in photopic conditions leaving ACHM patients with no functioning photoreceptors. However, research into scotopic vision in achromatopsia is limited and there is evidence to suggest that scotopic sensitivity may vary substantially between patients (Khan, Wissinger, Kohl, & Sieving, 2007; Nishiguchi et al., 2005; Sundin et al., 2000) and atypical dark adaptation curves have been found (Aboshiha, Luong, et al., 2014; Frey, Gordesch, Heilig, & Thaler, 1975; Simunovic, Regan, & Mollon, 2001). For example, Khan et al. (2007) reported on three sisters with a cone disorder caused by the *CNGB3* genotype and found reduced rod ERG b-wave amplitudes indicating loss of rod function. These results would suggest impaired scotopic vision, although full vision testing in scotopic conditions was not carried out.

Hess & Nordby (1986) looked at whether there was evidence of any residual cone activity in one ACHM patient. Any cone contribution would be expected to increase with increasing spatial frequencies and luminance. Therefore, it was speculated that if cones were active, any fall off in contrast sensitivity observed in the patient in mesopic and photopic conditions would be slower for higher spatial frequencies than lower ones. No evidence of this was found which supports the view of there being no functioning cones in ACHM.

[1] Calculated for a 5mm pupil

Results for spatial acuity are similar to those of contrast sensitivity, patients have been found to show normal scotopic acuity but this falls away sharply in high mesopic and photopic conditions (Hess & Nordby, 1986; Sloan, 1954). In a study of 4 patients (Sloan, 1954) the luminance at which acuity started to deteriorate ranged from 2-17 millilamberts (ml) (~6-54 cd/m^2). The limited acuity seen in ACHM can be attributed to the lack of cone photoreceptors which would usually provide visual input in photopic conditions. This is further supported by the fact that the maximum spatial acuity observed in ACHM is comparable to the acuity observed in scotopic conditions for those with healthy vision (van Nes et al., 1967).

1.5.3.5 Visual Pathways in Congenital Achromatopsia

While there is considerable heterogeneity in the morphology of the retina in ACHM patients, there is consensus that although cones are present they appear malformed and non-functioning (Harrison, Hoefnagel, & Hayward, 1960). This could lead to changes in the way the retina develops in ACHM patients and this does appear to be the case with the retina showing distinct differences compared to healthy controls. 50-80% of ACHM patients show foveal hypoplasia in which the usually cone-rich fovea has not formed its distinctive pit in the centre of the retina. It is also believed that the usual displacement of inner retinal cells does not occur. Further to this adaptive optics have shown what appear to be rods present in the fovea of one ACHM patient suggesting that patients may have some central vision (Liang, Williams, & Miller, 1997).

Although ACHM has been typically been classified as affecting cone photoreceptors there is also evidence to suggest that it may have long-term implications for other cells within the retina. Thiadens et al (2010) carried out optical coherence tomography (OCT) with ACHM patients and found thinning of the retinal pigment epithelium (RPE) in 18% of patients over the age of 40 years. Younger patients did not show these abnormalities. It is believed these changes to the RPE were due to non-functioning cone cells dying off with

age, impacting on the health of the RPE. However, changes to RPE was not associated with reduction in visual acuity in these patients.

In addition to the retinal changes that ACHM presents it seems reasonable to suppose that there could also be changes further along the visual pathway, within the brain, as a consequence of atypical visual input. Research into the impact of ACHM on the brain is relatively sparse. An fMRI experiment carried out with ACHM patients to assess whether they showed abnormal functional mapping of V1 found that the central region which only responds to cone input in controls, was activated by visual stimuli in ACHM patients (Baseler et al., 2002). This may demonstrate some reorganisation of the visual system, such that the lack of cone input throughout development led to regions of V1 usually specialised for cone input becoming responsive instead to rod input. Alternatively there may be rods present in the fovea in these patients which project to central V1. It is also possible that the usual developmental course was inhibited by the lack of cone input to V1 resulting in the region remaining unspecialised.

Some hypotheses can be made about how mid- and high-level vision could be affected in ACHM based on what is known about normal visual pathways. The proportion of input from the rods and cones to the magno- and parvo-pathways of the LGN varies. 90% of the input to the parvocellular system is colour sensitive and so reliant on information from cones. The remaining 10% of the signal to the parvocellular system comes from the summed input of the three types of cone photoreceptors as well as rod input (Kosslyn & Andersen, 1995). The magnocellular pathway is colour-blind, receiving information from both rod photoreceptors and the summed responses of cone photoreceptors. The reason behind the differences in colour sensitivity between magno- and parvocellular systems lies in the sensitivity of their cell receptive fields. Parvocellular cells have concentric receptive fields which demonstrate colour opponent responses, whereas, magnocellular cells have receptive fields which respond to a wide range of wavelengths irrespectively (Wickens,

2009). Studies in primates have suggested that rods feed predominantly into the magnocellular pathway providing a relatively weak input to the parvocellular pathway (Chen & Sampath, 2013; Grünert, 1997; Lee et al., 1997).

Based on this, it would be expected that ACHM patients would process more visual information via the magnocellular pathway than the parvocellular. Traditionally the magnocellular pathway was believed to feed into the dorsal stream, providing visuo-motor and spatial information, while the parvocellular pathway fed into the ventral stream, providing form and object information. While it is now known that there is considerable overlap between these two pathways, they are still largely believed to favour either form or motion perception. The dominance of rods, and presumably magnocellular mediated vision in ACHM, would therefore be expected to favour motion processing over form. However, in visual processes which require both form and motion information, such as biological motion, it is unclear exactly what the outcome may be.

1.5.4 Progressive Cone Dystrophies

Progressive cone dystrophies (PCD) cover both cone and rod-cone disorders affecting 1 in 30 000 to 40 000 worldwide (Thiadens et al., 2012). Rod-cone disorders, as the name suggests involve the early loss of rods as well as cones. Cone disorders on the other hand, predominantly affect cones although rods can be affected later on in the disease progression. For both types of PCD vision is typically normal until early adulthood at which point patients present with visual acuity loss. The course of PCD varies widely depending on the individual and genotype such that some patients will lose almost all vision and be declared legally blind while others will regain enough sight to be able to read and drive. The region of the retina affected can also play a part in the degree of functional vision maintained, although PCD predominantly affects central vision.

1.5.4.1 Clinical Features

The main symptoms of PCD mirror those of achromatopsia, namely reduced acuity, photophobia, central vision loss and loss of colour vision. Symptoms, however, can vary widely and PCDs are a heterogeneous group of disorders.

1.5.4.2 Genetics

The majority of PCD present an autosomal recessive genotype although autosomal dominant and x-linked varieties have been reported (Michaelides, 2014). Around 25 causative genes have been found to date (RetNet, the Retinal Information Network). The five patients reported on in this thesis held one of three genotypes, *GUCA1A*, *KCNV2-COD* and *RIMS1 (CORD7).*

GUCA1A encodes a variant of guanylate cyclase-activating protein (GCAP1). GCAP1 is expressed in both rods and cones and is required for synthesis of cGMP during the phototransduction cascade. *KCNV2* encodes a K^+ channel with mutations leading to disruption of channel subunits which is believed to impair photoreceptor function (Wu et al., 2006). *CORD7* is caused by mutations in the Rab3A interacting molecule (*RIMS1*) which is expressed in the brain and retina. *RIMS1* is believed to be important in synaptic transmission and plasticity (Michaelides et al., 2005).

1.5.5 Conclusion

The impact of cone disorders on the primary visual cortex and extrastriate regions are unclear. Previous research into patient groups with visual deprivation suggests that this leads to disruptions in the development of low-, mid- and high-level visual skills. However, cone disorder patients' vision is uniquely different from any of these patient groups given the fact that they have a very specific type of vision loss. The pattern of any extrastriate vision could therefore be expected to be different to that in previously studied groups.

Given that previous studies have found normal scotopic vision in ACHM patients it may be expected that extrastriate vision would also be comparable to controls scotopically. However, any departures from control performance within the scotopic range could indicate atypical cortical processing.

The effects seen in PCD on low-level vision appear similar to those of ACHM. Possible effects on extrastriate vision, however, may differ. Given the importance of early visual experience on the development of skills such as global form and motion perception, it is possible that differences may exist between those with stationary and progressive forms of cone disorder. If differences exist then this will suggest that cones are necessary for the typical development of these skills - however, if the two patient groups are similar to each other it suggests that extrastriate vision can develop without cone input.

The potential impact gene therapy may eventually have on extrastriate vision in cone dystrophies is unknown. The studies in this thesis aim first to discover how vision is affected pre-therapy, as this will shape predictions about what may happen after the treatment. If atypical results are found, this will suggest that recovery of visual function will depend on the visual system’s capacity to adapt and demonstrate plasticity in response to new visual experiences.

Chapter 2. GENERAL METHODOLOGY

2.1 BEHAVIOURAL TESTS

2.1.1 Introduction

Behavioural psychophysics refers to the relationship between physical stimuli and the subjective perception of an individual. By recording an individual's response to a stimulus as it varies along some dimension we can gain an insight into how the brain processes sensory experiences. In the case of visual psychophysics, manipulating factors such as contrast, luminance and spectral composition, and recording the associated changes in perception, allows us to carefully map the sensory output of our visual system based on the physical input.

One method widely employed in visual psychophysics is the forced choice paradigm, in which a participant is required to select the presence of a stimulus amongst multiple options, with the intention of creating a bias free measure. For example a participant may be required to select a target stimulus when presented alongside a distracter. Correct and incorrect responses can then be plotted at different levels of the stimulus and a function fitted to describe how perceptual sensitivity changes in response to physical changes in the stimulus.

All the behavioural tasks described in this thesis use the forced choice paradigm to calculate participants' threshold. Further details of each individual test and the method of calculating the threshold can be found below.

2.1.2 Overview of Task Design

Four behavioural tasks are used throughout this thesis: detection of coherent form, coherent motion and biological motion, and a contrast sensitivity test.

The behavioural tasks employed a two-alternative forced choice (2AFC) design in which the target was displayed on one half of a screen and a distracter on the other. The participant's task was to judge the side containing the target. Stimulus intensity, such as coherence or contrast, varied along a staircase. Coherent form, motion and biological motion tests used the Psi adaptive method (Kontsevich & Tyler, 1999) which estimated the 75% threshold, while the contrast sensitivity test used a closely related Bayesian method (Lesmes, Lu, Baek, & Albright, 2010),

2.1.3 Psi Adaptive Method

The Psi adaptive method (Kontsevich & Tyler, 1999) uses a Bayesian adaptive approach to estimate the slope and threshold of a psychometric function. It is a highly efficient method that is designed to test, on each trial, the point on the psychometric function most informative for distinguishing between possible values for the slope and threshold parameters. The shape of the psychometric function to be fitted is set beforehand (e.g. logistic). This generally has two free parameters, with two additional fixed parameters for guess and lapse rate (see below). The form, motion and biological motion tests used a logistic function. As an adaptive staircase, the Psi method uses information about previous trials to select future stimulus intensities and adapts parameter estimates as it does so. Stimuli intensities are selected based on their predicted ability to minimize entropy in the posterior distribution. Entropy is calculated based on the given probability of a scenario:

$$\mathrm{H} = \sum_{i} p_i \log_2 p_i$$

Where H is the entropy, *i* is the parameter being considered and p_i is the probability for each parameter.

In the case of the Psi method, the entropy is calculated based on the probability of the slope and threshold being correct, as predicted based on the posterior distribution:

$$\mathrm{H} = \sum_{a}\sum_{b} p(a,b)\log_2 p(a,b)$$

Where *a* = threshold estimate, *b* = slope estimate, *p* = probability.

With each trial, the Psi method calculates the entropy for each stimulus intensity and selects the intensity with the lowest entropy for the next trial. The overall aim of the Psi method is to gradually reduce the uncertainty of the parameter estimates. Other parameters including the guess rate and lapse rate are fixed and can be set by the user. The guess rate is the probability of being correct by chance and was set to 0.5 for these experiments due to the 2-AFC design (participants had a 50% chance of guessing the target stimulus). The lapse rate is the proportion of trials on which failures unrelated to perception are expected (e.g. lapses of attention or incorrect button-presses). This was set to the standard value assumed by the Psi method of 0.025 (Prins, 2012).

2.1.4 Stimuli Presentation

All stimuli described here were generated in Matlab using Psychophysics Toolbox (Brainard, 1997) and displayed on a Mitsubishi Diamond Pro 22" CRT monitor with a frame rate of 60 Hz. Stimuli were viewed at a distance of 60 cm creating a display area of 37° x 28°.

2.1.5 Coherent Form and Motion Stimuli

2.1.5.1 Background

Coherent form and motion stimuli have been used to study global visual processing since the 1980s. Coherent form stimuli were originally generated as Glass patterns (Glass,

1969), a form of Moiré pattern (see Figure 2.1). When a series of random dots are copied and superimposed on themselves then rotated a by a small degree the resulting image carries the impression of a circular form. These patterns have been used extensively to study form perception (E.g. Glass & Switkes, 1976; Lewis et al., 2002; Lewis et al., 2004; Prazdny, 1984; Smith, Bair, & Movshon, 2002; Smith et al., 2002; Wilson, Wilkinson, & Asaad, 1997). The form stimulus used in this thesis works on a similar principle but used line segments rather than dot pairs.

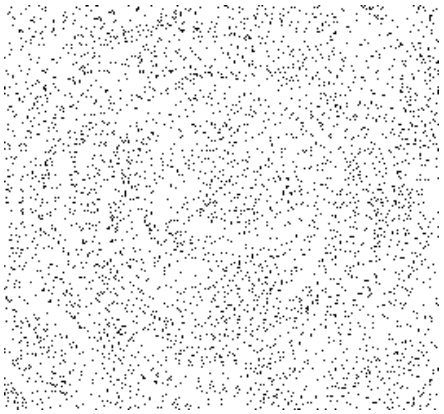

Figure 2.1. Glass pattern used in the study of coherent form perception.

Coherent motion stimuli have generally been generated in the form of random dot kinematograms (RDK) (Cleary & Braddick, 1990; Newsome & Pare, 1988; Smith, Snowden, & Milne, 1994; Snowden & Braddick, 1989; Watamaniuk, McKee, & Grzywacz, 1995). These work on a similar principle to glass patterns with a display of random dots being displaced by a small degree to create apparent motion. RDKs are the most common stimulus choice when studying coherent motion perception. These can be used to create a whole range of motion types including; rotational, translational, contracting and expanding.

2.1.5.2 Thesis Coherent Form and Motion Stimuli

Coherent form and motion stimuli used in this thesis were generated in Matlab from code written by John Wattam-Bell (see Figure 2.2). Stimuli consisted of short arc segments aligned around a central point to create a concentric texture. For both the form and motion stimuli each arc segment consisted of 8 dots. For the form stimuli these dots were plotted simultaneously while for the motion stimulus then were plotted successively, creating motion along the arc trajectory.

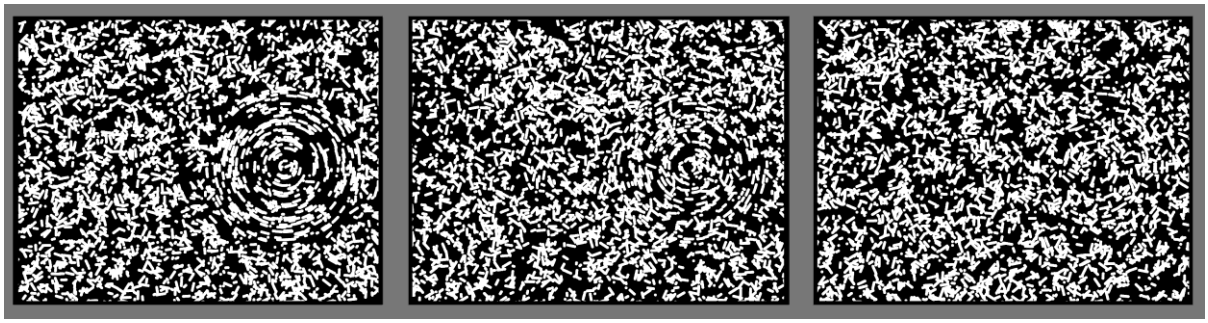

Figure 2.2. Example of the form and motion task. Stimuli from left to right show 91%, 60% and 24% coherence (with coherent stimulus on the right). Form stimuli are shown here but also demonstrate the motion task in which each line segment represents the motion trajectory of a single dot.

Coherent form and motion stimuli consisted of 2000 white dots, each with a 6 pixel diameter and 0.29° visual angle, plotted against a black background. To create the motion stimuli 8 dots were plotted in successive frames creating motion along an arc trajectory at 8.6 deg/sec, with a lifetime of 133 msec. Within each frame 1/8 dot lifetimes were randomly restarted, creating the overall impression of multiple motion trajectories of varying length. Form stimuli were matched to the motion stimuli, plotting dots from individual frames simultaneously to create stationary short arc segments. Line segments were 1-8 dots in length with an average length of 1.3°. The starting locations of dots and of line segments were randomly distributed across the display area for each trial. In each case, coherently

plotted elements were arranged in a circular structure with a common centre of curvature. This produced a region of concentric structure subtending 16°. Outside this region, the arcs were randomly oriented.

The task employed a two-alternative forced-choice (2AFC) design in which coherent form or motion was displayed on one side of the screen, centred 10° from the screen centre. The participant's task was to judge which side contained coherent form or motion. Trials varied in their level of coherence by varying the ratio of coherent to random elements within the circular target region. Participants were asked to fixate on a white central cross while stimuli were presented, at random, on the left or right of fixation as shown in Figure 2.2.

Stimuli were presented for 1 second after which time a black screen appeared. The participant then had as much time as they wanted to indicate the location of the target using either a right- or left-hand button. Participants were presented with 30 trials per staircase from which their 75% threshold was estimated using the Psi method (Kontsevich & Tyler, 1999). Three runs of each staircase were repeated for each test and the average threshold across runs was calculated.

2.1.5.3 Comparability of Form and Motion Stimuli

We used coherent form and motion stimuli that were matched, as in previous studies (Atkinson & Braddick, 2005; Wattam-Bell et al., 2010), so that the regions of the visual field over which local form and motion information needs to be integrated are directly comparable. In other important respects the stimuli cannot be made directly comparable – for example, because the motion case requires spatial integration over time, the moving stimulus is a dot (that describes a line over time). The stimuli thus have different spatial (and spatio-temporal) content – e.g. the motion stimuli (dots) have less low-spatial frequency information than the

form stimuli (lines), although they have also have temporal information that the form stimuli do not. Because of the presence of such differences, our analyses do not treat the stimuli as exactly matched in all respects except for the single difference of having form- vs. motion-related coherence.

2.1.6 Biological Motion Stimuli

2.1.6.1 Background

Biological motion is studied using point light displays (PLDs), originally created by Johansson in the 1970s (Johansson, 1973). PLDs are created either from real footage or computer algorithms but always with the same purpose – to display the motion of a living organism reduced down to a select few points of light attached to key joints in the body. The aim of this is to strip the biological motion of all extraneous cues, other than the motion itself. As a result, PLDs appear as random dots when stationary, only becoming recognisable when motion is applied (see Figure 2.3).

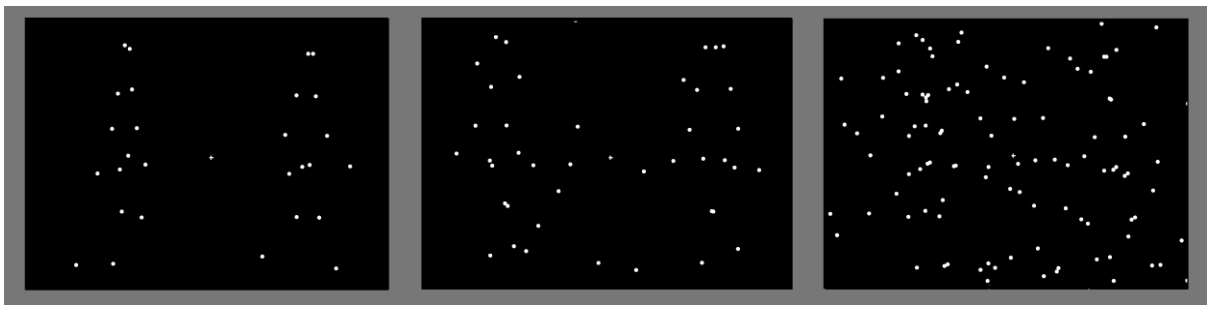

Figure 2.3. Example of the biological motion stimulus display at 93%, 50% and 15% signal to noise ratio. Biological motion is present on the right of these stimuli, scrambled motion on the left.

Biological motion stimuli for this thesis were generated using Cutting's Algorithm (Cutting, 1978). This is a widely used algorithm (e.g. Hirai, Fukushima, & Hiraki, 2003; Hirai &

Hiraki, 2005; Mather & Murdoch, 1994; Neri, Morrone, & Burr, 1998; Vaina, Solomon, Chowdhury, Sinha, & Belliveau, 2001) which allows the creation of a variety of human movements.

2.1.6.2 Thesis Biological Motion Stimuli

Stimuli consisted of point-light figures made up of 14 white dots each with a visual angle of 0.27^{o} and moving at an average speed of 5.8 deg/sec. Figures walked on the spot as if on a treadmill and filled an area subtending 15.2^{o} x 5.7^{o}. The figure was presented from one of five possible angles; straight on, to the left, to the right, diagonally left and diagonally right. This was intended to minimise habituation and to reduce the risk of participants adopting specific strategies to detect the motion such as focusing on the location of individual light points.

Stimuli were presented alongside a scrambled version of the figure (see Figure 2.3). Scrambling was achieved by randomising the starting position of the dots and the phase of the joint angles. The angle at which the figure was presented was matched on each trial between the biological and scrambled figure. Participants were instructed to indicate the side of the display containing the unscrambled biological motion.

As with the form and motion stimuli, participants viewed 90 trials (3 runs of 30 trials, estimated threshold averaged across the runs). Figures were embedded within random noise dots as shown in Figure 2.3. Noise dots moved at the same average speed as the biological motion dots (5.8 deg/sec) and were drawn at random from the individual motion trajectories of biological motion dots. The signal to noise ratio (i.e. proportion of noise dots) on each trial varied based on the Psi adaptive method and the 75% threshold was estimated.

2.1.7 Contrast Sensitivity Stimuli

In addition to coherent form and motion and biological motion, it was important to gain some idea of participants' early-level visual processing. This would allow comparison between early-level visual processing and higher level perception in order to establish whether any effects could be explained by early-level visual deficits.

Measurement of contrast sensitivity has traditionally involved lengthy testing with trials of different contrast and spatial frequency in order to plot the contrast sensitivity function. A contrast sensitivity function plots contrast sensitivity (1/threshold) as a function of spatial frequency. Tests have typically involved estimating a contrast threshold for individual spatial frequency gratings requiring ~100 trials per spatial frequency. This can add up to ~500-1000 trials depending on the number of spatial frequencies tested.

A relatively new method known as the quick CSF (qCSF) (Lesmes et al., 2010), allows a complete contrast sensitivity function to be mapped with as few as 100 trials. It does this using a Bayesian adaptive method to estimate parameters of the CSF in the form of a truncated log-parabola. Different forms of CSF exist but the qCSF method favours the truncated log parabola because it is able to successfully describe the low frequency plateau seen in CSFs. A more detailed justification for the truncated log-parabola, and a full account of the method, is given in Lesmes et al. (2010). The four parameters estimated by the qCSF are peak gain (γmax), peak spatial frequency (fmax), bandwidth (β) which is the full width at half height, and truncation (δ).

The log-parabola is defined by:

$$S'(f) = \log_{10}(\gamma_{max}) - k\left(\log_{10} f - \frac{\log_{10}(f_{\max})}{\beta'/2}\right)^2$$

$k = \log_{10} 2, \beta = \log_{10} 2\beta$

The truncation factor is then added for low spatial frequencies:

$$S(f) = S'(f) \qquad f \geq f_{max}$$

$$S(f) = \log_{10}(\gamma_{\max)} - \delta, \qquad f < f_{max} \text{ and } S'(f) < \gamma_{max} - \delta$$

The qCSF method fits the four free parameters (γmax, fmax, β, δ) mentioned above based on a Bayesian adaptive method. It does this by updating the posterior probability (the probability based on the existing evidence) for each parameter at each trial and selecting future stimuli based on their ability to minimise uncertainty surrounding those parameters (see Lesmes et al. (2010) for a full account of the procedure). The qCSF method is similar to that of Psi adaptive method (Kontsevich & Tyler, 1999) but is designed to give greater precision over fewer trials. Hou et al. (2010) provide an in depth comparison of the qCSF to other adaptive methods, including Psi, showing its superior ability to estimate the CSF shape using 100 trials or less.

A test was specifically designed for use in this thesis using the qCSF method. Details of the piloting of this test can be found in appendix IV.

Stimuli consisted of a Gabor patch, a sinusoidal grating, set in a Gaussian envelope with standard deviation set to a constant 6°. Gabors were presented 10° to the left or right of fixation. Gabors varied in spatial frequency and contrast from trial-to-trial based on the qCSF method.

Stimuli were presented for 5 seconds and participants indicated with a button press whether the stimulus was to the right or left of fixation. After 100 trials the test ended and the contrast sensitivity function was mapped. Summary statistics such as the peak contrast sensitivity and cutoff spatial frequency (the spatial frequency at which contrast sensitivity was equal to 1) could then also be estimated.

2.2 STEADY STATE VEPS

2.2.1 Introduction

Electroencephalogram (EEG) recording is a well-established non-invasive investigative technique which provides excellent temporal information on cortical processing. The technique utilises electrodes placed on the scalp which are able to record electrical activity from the brain related to neuronal activity. The neuronal responses picked up by EEG are generated principally by post-synaptic potentials (PSPs) of pyramidal cells (Olejniczak, 2006).

Visual evoked potentials (VEPs) can be classed into two categories – transient and steady state. Transient VEPs consider epochs in the temporal domain, with stimuli sufficiently spaced out to create individual time locked neural responses. Steady state VEPs (SSVEPs) work in the frequency domain using rapidly alternating stimuli designed to elicit oscillating neuronal responses at set frequencies. The experiments described in this thesis all employ a steady-state design.

SSVEPs were first reported by Adrian & Matthews (1934) who found that the brain produced rhythmic waves at the same frequency as a flickering light. The Fourier transform can be used to break down the VEP signal into different frequencies including the fundamental frequency (the frequency at which the stimulus alternates) and its

harmonics. This technique has been used extensively in VEP studies (Ales, Farzin, Rossion, & Norcia, 2012; Angelelli, de Luca, & Spinelli, 1996; Braddick, Wattam-Bell, & Atkinson, 1986; Campbell & Maffei, 1970; Harris, Atkinson, & Braddick, 1976; Heinrich & Bach, 2003; Morrone, Burr, & Fiorentini, 1993; Pastor, Artieda, Arbizu, Valencia, & Masdeu, 2003; Victor, Conte, Burton, & Nass, 1993; J. Wattam-Bell et al., 2010; John Wattam-Bell, 1991).

2.2.2 SSVEP Data Recording

2.2.2.1 The EGI System

EEG was recorded using the EGI 300 system (Electrical Geodesics Inc, Eugene, Oregon). The EGI system consists of a 128-electrode HydroGel Geodesic Sensor Net. Seven of the EGI electrodes are designed for electrooculogram recording so were excluded in these experiments leaving a total of 121 electrodes plus Cz (vertex). Prior to fitting, the EGI net was soaked for five minutes in a warm saline solution (1.5M KCl). This was absorbed by sponges surrounding the electrodes to enhance the electrical conductance. Participants had their head circumference measured and were fitted with either a medium (55-58 cm) or large (<58 cm) net. A rostral-caudal centre point was marked on the participants' scalp using a soft crayon and this was used to accurately position the net, ensuring the central electrode (Cz) was placed over this point. The net was then adjusted to ensure a good fit. The VEP experimental setup, including a participant fitted with the net, can be seen in Figure 2.4.

Figure 2.4. VEP experimental setup.

2.2.2.2 Impedance

Impedance refers to the resistance as measured in kΩ recorded at each electrode. Impedance is measured before recording commences and electrodes with high readings are adjusted to bring the impedance down. This is done by applying extra solution under the electrode using a pipette. High impedance is usually the result of poor contact between the electrode and scalp due to hair/ hair products, sweat or lack of conducting fluid/gel. The EGI system recommends impedance to be reduced to below 50 kΩ for non-clinical and 100 kΩ for clinical populations. For our studies we had both clinical and non-clinical participants and impedance was therefore set at an intermediary of 90 kΩ. In reality, electrode impedance was nearly always below 50 kΩ for both clinical and non-clinical participants.

2.2.2.3 Filtering

All filtering in the experiments described here was based on standard SSVEP practice (Odom et al., 2010; Picton et al., 2000). Filtering aims to increase the signal to noise ratio of the data by removing frequencies which are likely to be contaminated by electrical and electromyogram (EMG) noise and unlikely to contain VEP data.

Data was first digitized at 250 samples per second. This translates the continuous ERP signal into discrete samples for further analysis. At the same time, the ERP hardware carried out anti-aliasing on the ERP signal, supressing frequencies above the Nyquist Frequency (125 Hz). A low pass filter was then applied (20 Hz, 12 dB/ octave).

2.2.2.4 Artefact Rejection

As well as filtering to remove unwanted noise from the data, whole channels and epochs can be removed if they are deemed to be too noisy. This further increases the quality of the data but care has to be taken to avoid being either too stringent, which can lead to a loss of informative data, or too lax, which can lead to noisy data containing artefacts.

For the data within this thesis, channels were excluded if the standard deviation of the raw signal, throughout the recording session exceeded 800μV. VEP data was then divided into 1 second epochs (two stimulus cycles at 2 Hz), excluding any epochs with a maximum voltage excursion greater than ±100 μV. Channels containing fewer than 100 artefact-free epochs, out of a total of 200, were discarded.

2.2.2.5 Averaging

During data recording the vertex was used as a reference. Post data recording and filtering, each channel was re-referenced offline to an average reference. Using the

average as a reference has the advantage of providing a good estimate of the absolute voltage at each electrode. Neural sources are dipolar in nature and the overall sum of all positive and negative fields across the scalp should therefore equal zero. A dense and wide reaching array such as the one used here provides a good estimate of the true zero value, minimising the bias which would result from localised electrode arrays or from a single reference point. Referencing to the average therefore provides a powerful tool to subtract noise from the EEG signal.

2.2.3 SSVEP Stimuli Generation

Coherent form and motion SSVEPs were carried out using stimuli used previously in VEP research (Wattam-Bell et al., 2010). Biological motion SSVEPs were attempted but no significant brain response was generated. This may be due to the longer time taken to detect biological motion being ill-suited to a steady-state design. Details of the design and piloting of biological motion VEPs can be found in appendix III.

As with the behavioural tests, all stimuli were generated in Matlab using Psychophysics Toolbox (Brainard, 1997) and displayed on a Mitsubishi Diamond Pro 22" CRT monitor with a frame rate of 60 Hz.

Stimuli were matched in design to those used in the behavioural tests, containing 2000 white dots, each with a 6 pixel diameter (0.29° visual angle), plotted against a black background. Unlike in the behavioural stimuli however, these were displayed centrally and filled the entire display (37° X 28°), with no active task required. Participants instead passively viewed the form or motion stimuli.

The display alternated between 100% coherence and 0% coherence at a rate of 4 reversals/ sec (Figure 2.5). In the coherent phase, the line segments or dots aligned to

create a circular form or rotational motion respectively. In the incoherent phase, line segments or dot trajectories were orientated randomly within the display.

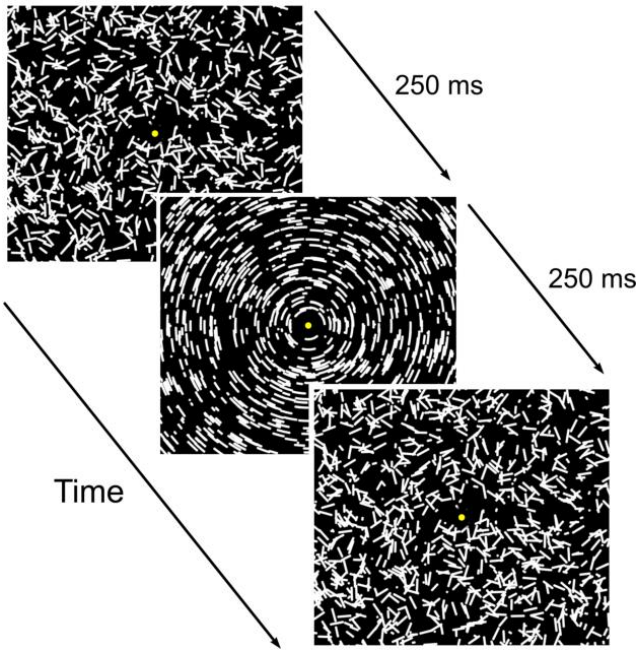

Figure 2.5. Example of the coherent form stimuli alternating between 100% coherence and 0% coherence. The figure also demonstrates the motion stimulus in which the arcs represent the trajectories of moving dots.

2.2.4 SSVEP Recording

Stimuli were viewed binocularly at a distance of 60 cm. Participants were instructed to remain as still as possible during the EEG recording. A fixation point was present in the centre of the display throughout the experiment and participants were instructed to fixate this.

Form and motion stimuli were presented in separate runs lasting ~5 minutes each. Each run consisted of 20 blocks per test (form, motion). Each block included 20 cycles (40 reversals) lasting 10 seconds.

2.2.5 F1 and F2 as Measures of Global and Local Processing

The fundamental frequency (F1) represents responses at the same frequency as the stimulus cycle. A significant F1 therefore represents activation in response to the onset of global structure in the stimuli, with an asymmetric response to coherence onset vs offset.

A significant F2 represents responses to changes in the stimulus configuration brought on by every stimulus switch. With each stimulus transition the magnitude of local orientation change is uniformly distributed, which predicts the same average response to local changes for incoherent-coherent and coherent-incoherent transitions. F2 therefore includes responses to local changes in the stimulus configuration. Neural responses to global changes may also be present in F2, however only F1 isolates a signal arising from global changes.

The basis of F1 as a measure of global processing was verified by Braddick et al (2006) who found that the amplitude of F1 dropped to zero as the coherence was reduced to 0%, for both form and motion stimuli, while F2 amplitudes remained consistently strong. As well as this, a control experiment designed using the present setup described was carried out and is described in appendix V. This found that F2 responses were maintained when stimuli were set to 0% coherence but F1 responses were minimal, further confirming F1 as a global response.

2.2.6 T^2_{circ} Statistic

Fourier analysis was used to extract SSVEP amplitudes and phases at the fundamental frequency (F1=2Hz form/motion) and the second harmonic (F2=4Hz form/motion). The presence of a significant response at each harmonic can be tested with the T^2_{circ} statistic (Victor & Mast, 1991) in both first-level (individual) and second-level (group) analyses, as described in Wattam-Bell et al (2010). This statistic is designed specifically for analysing

SSVEPs, and provides a measure of the signal to noise ratio. The T^2_{circ} statistic works as a 2-D t-test, taking into account both the phase and amplitude of the signal at each harmonic. A circular 95% confidence limit is generated around the tip of the mean amplitude vector on a sine-cosine plot (see Figure 2.6). The ratio between the response amplitude and the radius of confidence limit is calculated. If the ratio is less than one, this means that the confidence limit overlaps the origin and the response is taken as not significantly different from noise. This is demonstrated in Figure 2.6.

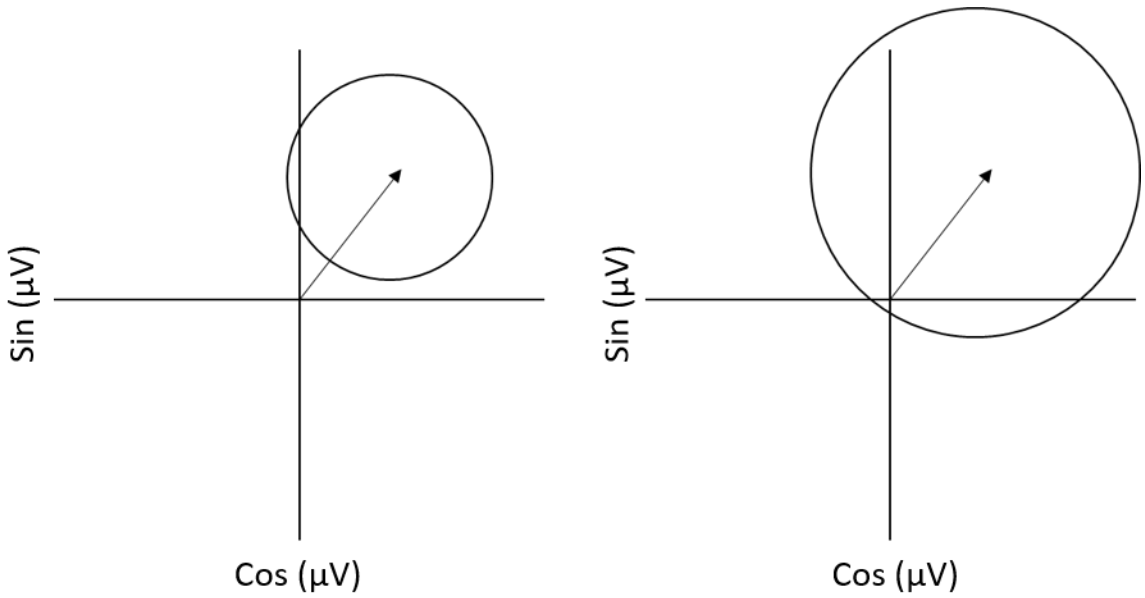

Figure 2.6.Example visualisation of the T^2_{circ} statistical test. The mean amplitude vector is shown on a sine-cosine plot surrounded by the 95% confidence bound generated by the T^2_{circ} test. The figure on the left shows a significant response in which the confidence bound does not encompass the origin.

2.3 STUDY ETHICS

All research was carried out with full ethical approval from the relevant ethics board. For control participants ethical approval was given by the UCL Ethics Board. Research involving patients was conducted under ethical approved given by the NHS Research Ethics Committee.

For each study discussed within this thesis participants were given an information sheet before data collection commenced. Once participants had had a chance to read the information sheet and ask any questions they had regarding the research, informed consent was taken. Information sheets and consent forms are shown within appendix I.

All participants were assigned a unique study ID which consisted of a number, and contained no identifiable information. This was used in all data processing and storage.

Patients gave their time freely but were reimbursed for their travel expenses (see appendix I for participant payment forms). Control participants were paid £7.5 an hour for their time but travel expenses were not reimbursed. This was in line with the ethical approval given for participant category (patient or control).

2.4 DATA ANALYSIS

Statistical analyses on behavioural and VEP data were carried out in SPSS (*PASW STATISTICS*, 2009) and Matlab (*MATLAB*, 2012) version R2012b (32-bit). Plots were generated in Matlab (*MATLAB*, 2012) and Microsoft Excel.

Chapter 3. COHERENT FORM, COHERENT MOTION AND BIOLOGICAL MOTION PERCEPTION UNDER BLUR

3.1 INTRODUCTION

The current study aimed to look at the role of spatial frequency content in the perception of coherent form, motion and biological motion. The patient populations described within this thesis all have reduced acuity and contrast sensitivity. To address the contribution of high spatial frequencies and contrast to global perception, normally sighted participants completed behavioural and SSVEP tests of global form, global motion and biological motion perception under varying degrees of blur. The blur was created with a diffuser, placed in front of the display monitor which filtered out high spatial frequencies and lowered contrast. Results from this study will help build hypotheses about patient vision and allow comparisons to be made between those with temporary visual impairments and those with long-term sight loss. If patient populations demonstrate deviations from the pattern of results seen in these controls it may represent long-term adaptations due to extended periods of low vision.

Previous research into the influence of high spatial frequency loss on form and motion perception has focused on testing psychophysical thresholds whilst participants wear blurring lenses. By fitting participants with positive diopter lenses it is possible to filter out the majority of high spatial frequencies a participant is exposed to. This optical blur can therefore be used to simulate reduced sensitivity to high spatial frequencies (poor visual acuity).

Zwicker et al (2006) investigated the effects of positive diopter lenses, ranging from +0.75 to +4.00 diopters (D), in a psychophysical experiment of global form and motion processing. They found that while global form coherence thresholds were reduced with increased blur, global motion thresholds were unaffected (Zwicker, Hoag, Edwards, Boden, & Giaschi,

2006). This suggests that form perception may be more reliant on high spatial frequencies than global motion perception.

Braddick et al (2007) examined the effects of optical blur, induced with positive diopter lenses, on form and motion coherence thresholds. Participants were required to identify either rotational motion or stationary concentric circles at varying coherence levels in a 2AFC task. Up to +5D of blur did not significantly increase thresholds from baseline; however at higher levels (+7D or more) impairments were seen (Braddick, Akthar, Anker, & Atkinson, 2007).

The interaction between spatial frequencies and dot displacement in motion stimuli also appears to be important. Braddick and Cleary (1990) found that the upper displacement limit (d_{max}) increased when high spatial frequencies were removed from random dot kinematograms. Mirroring this Barton et al (1996) found that blur equivalent to +3.25D worsened direction discrimination when dot displacement was low (less than 16´) but conversely, discrimination was increased when displacement was high (greater than 21´). This suggests that high spatial frequencies may aid global motion perception but only when dot displacement is relatively low (Barton, Rizzo, Nawtrot, & Simpson, 1996; Cleary & Braddick, 1990). This highlights the complexity of the global motion system and the need to take multiple aspects of stimuli into consideration when determining the influence of different spatial frequencies.

Previous studies into the effects of optical blur have focussed on behavioural tests, however another method widely employed in developmental and clinical research is EEG. Participants were therefore tested with both behavioural and EEG tests using the methodologies described in chapter 2 (General Methods).

The current study examined the impact of blur on both behavioural measures of sensitivity to coherent form, motion and biological motion and VEP measures of coherent form and motion. Optical blur created with positive diopter lenses as used in previous studies (Barton et al., 1996; Braddick et al., 2007; Zwicker et al., 2006) does not have a smooth modulation transfer function, resulting in some high spatial frequencies still being perceptible, albeit with phase distortions ('spurious resolution'). To address this, the current study used a diffusing sheet which acts as a low pass filter. This method has been used extensively in vision research as a means of creating blur (Enoch & Williams, 1983; Essock, Williams, Enoch, & Raphael, 1984; Legge, Pelli, Rubin, & Schleske, 1985; Westheimer & McKee, 1980; Williams, Enoch, & Essock, 1984). This study also tested a wider range of blur than used in the previously described studies (Barton et al., 1996; Braddick et al., 2007; Zwicker et al., 2006), in order to measure the impact of the large degree of blur that would be experienced by some visually impaired populations, including the cone disorder patients described in chapters 5&6.

3.2 METHODS

3.2.1 Participants

Twenty adults (mean age 23.8 years, standard deviation 3.4) participated in the study. All participants had normal or corrected to normal vision and no known neurological problems. Participants were given an information sheet and written informed consent was given by each participant before the experiment commenced.

3.2.2 Tests Completed

For the behavioural tests participants completed coherent form, coherent motion, biological motion and contrast sensitivity tests. For the SSVEP tests participants completed coherent form and coherent motion tests. A biological motion SSVEP was piloted but unsuccessful. Details of this can be found in appendix III.

Details of the stimulus design, task procedure and SSVEP data handling can all be found in the chapter 2 (General Methods). All tasks were carried out as described there with additional features described below.

3.2.3 Visual Blur

Blur was achieved using a diffuser placed over the screen, acting as a low pass filter. The filter consisted of an A3, 800 micron polypropylene sheet (Gerprint, Peru) mounted onto a frame which stood in front of the monitor.

The distance between the filter and the screen was varied to create different levels of blur. The distances were selected to allow comparison with previous studies using dioptric blur (Barton et al., 1996; Braddick et al., 2007; Zwicker et al., 2006). To do this, three positive dioptre lenses were initially selected; +2.5, +5.5 and +10. Three participants completed a

binocular letter acuity chart at 60 cm on the test monitor whilst wearing each lens. The chart consisted of lines of letters selected at random from DHKNORSVZ and presented in the Sloan acuity font (Pelli, Robson, & Wilkinson, 1988). Letters were presented in lines of four with each line presenting successively smaller letters. When participants incorrectly identified two letters in a row the test was stopped and their acuity was calculated in LogMAR based on the viewing distance and letter size. After assessment with the lenses, participants had their acuity assessed using the filter at 0.5 cm distances from the monitor and the distance producing a comparative acuity to the dioptric blur was noted. Based on this, distances of 0 cm, 2cm and 3 cm were found to reduce acuity to a comparable degree to the +2.5, +5.5 and +10 dioptre lenses respectively.

Acuities for each blur level are reported in Table 3.1. Participants also had their acuity measured with no blur, however, due to limitations of the monitor all results were at ceiling with the highest recordable acuity being 0.26 LogMAR.

	0 cm	**2 cm**	**3 cm**
Mean acuity (LogMAR)	0.53	0.88	1.20

Table 3.1. Average visual acuity of three participants under the three blur conditions.

In order to further assess the impact of blur on acuity and contrast sensitivity, the same 3 participants had their contrast sensitivity function measured at each blur level using the qCSF test described in chapter 2 (General Methods).

Participants completed 100 trials at a distance of 60 cm, from which their contrast sensitivity function was plotted. Figure 3.1 shows contrast sensitivity functions for the three participants at each blur level. This demonstrates that there was a marked loss of contrast sensitivity at higher spatial frequencies, confirming that the diffuser was acting as a low-pass filter.

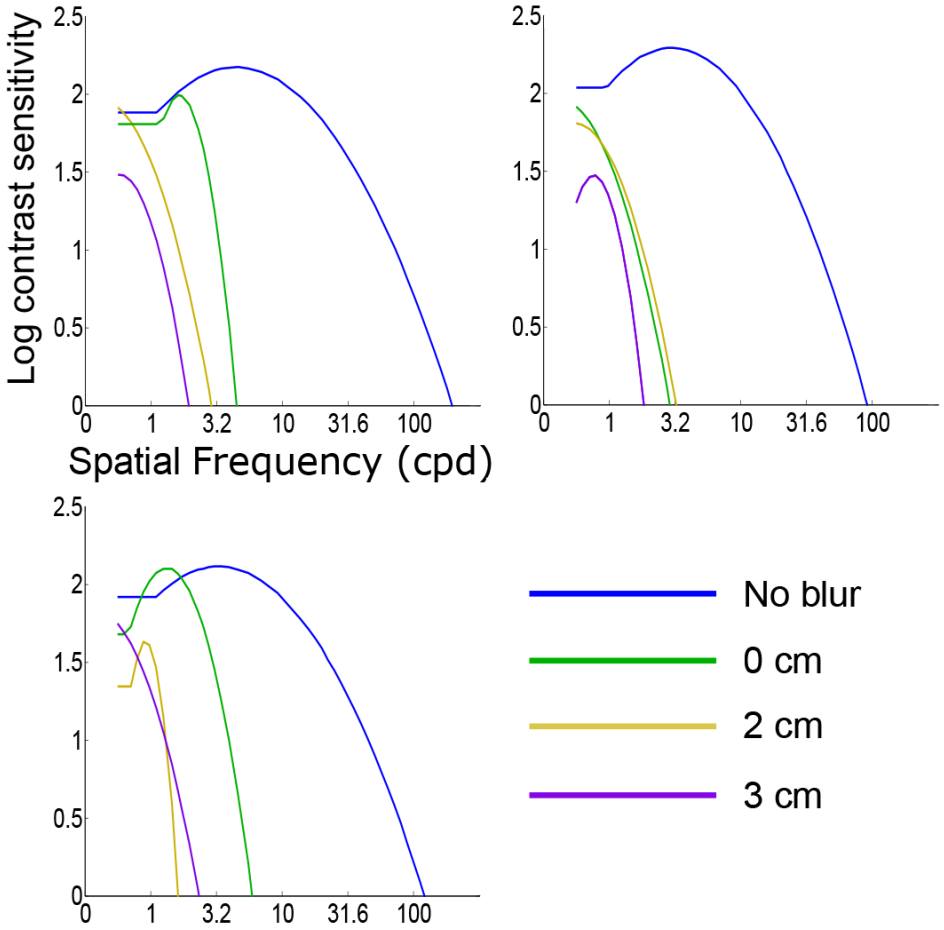

Figure 3.1. Contrast Sensitivity Functions for 3 individuals under the different blur levels. All three participants could detect the highest spatial frequency achievable with the display (13.75 cpd) in the no blur condition.

3.3 RESULTS

3.3.1 Behavioural Tests

The Shapiro-Wilk test was carried out on all behavioural data to assess whether it was normally distributed (Table 3.2). This revealed some data did not fit a normal distribution and as such all data was log transformed before analyses were carried out.

		Original	Transformed
Form	No blur	0.34	0.99
	0 cm	0.93	0.77
	2 cm	0.07	0.05
	3 cm	0.55	0.43
Motion	No blur	**p<0.01****	0.05
	0 cm	**p<0.01****	0.18
	2 cm	0.98	0.98
	3 cm	0.28	0.98
Biological Motion	No blur	**p<0.01****	0.96
	0 cm	**p<0.01****	0.99
	2 cm	**p=0.01****	0.98
	3 cm	**p<0.01****	0.22

*Table 3.2. p-values from the Shapiro-Wilk test of normality. Values are given for group results of each test in each light condition, in original data and log-transformed data. P-values <0.05 (shown in bold *) and <0.001 (shown in bold **) indicate that the distribution departs significantly from the normal.*

Performance on all three tests worsened with increasing blur, however there were considerable differences in how much each test was affected as shown in Figure 3.2. Performance on both global form and global motion tasks was significantly reduced as a function of blur (form: $F(3, 57) = 367.680$, $p < 0.001$; motion: $F(3, 57) = 29.079$, $p < 0.001$). However, biological motion performance was not significantly reduced by blur ($F(3, 57) = 2.629$, $p = 0.059$).

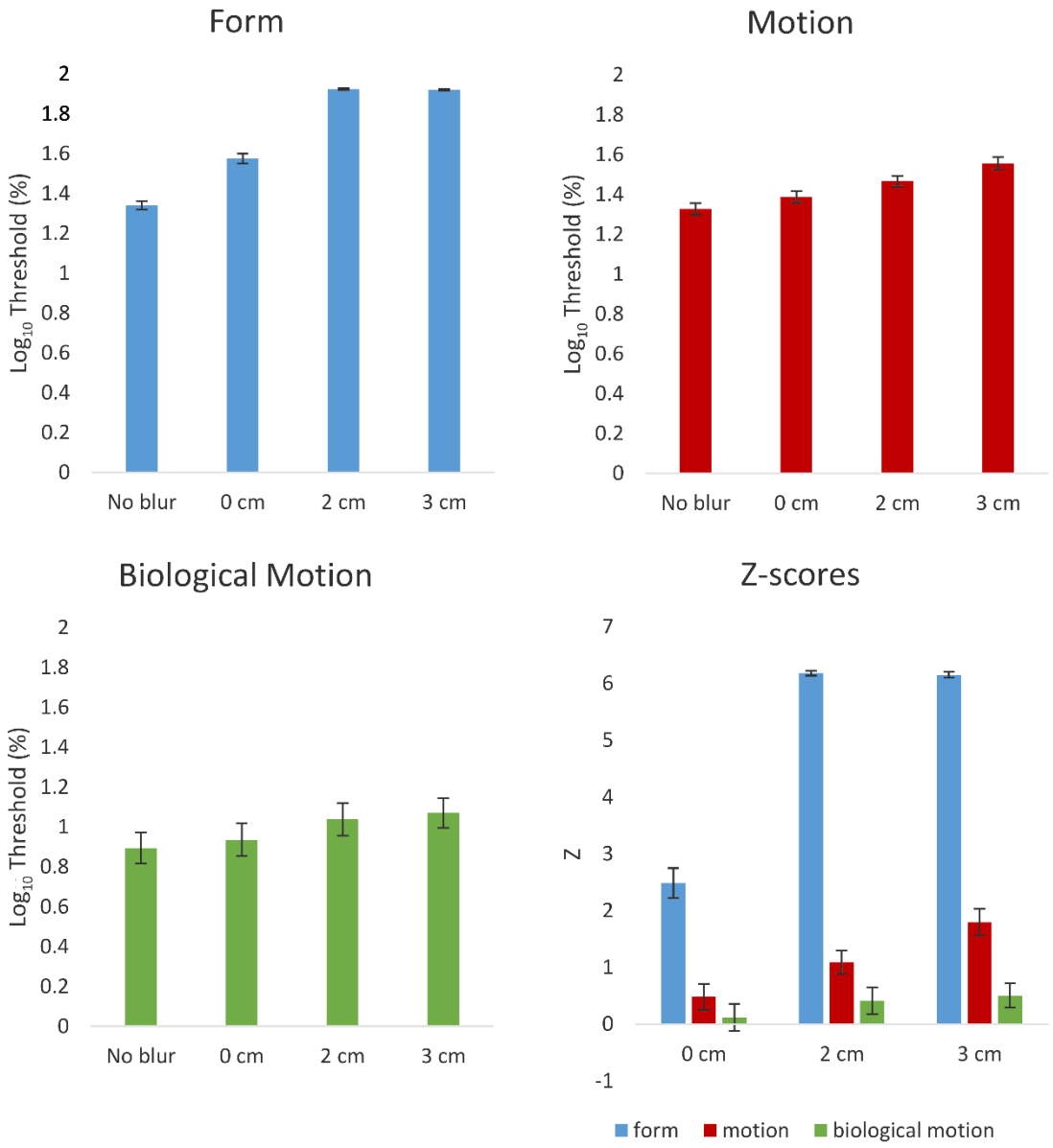

Figure 3.2. Form, motion and biological motion log thresholds under 4 levels of blur as well as z-scores for the three tests. Error bars represent the standard error of the mean.

Z-scores were calculated for each level of blur against the baseline condition of no-blur to allow comparison between the three tests. These demonstrate that biological motion and coherent motion were relatively unaffected by blur in comparison to form (Figure 3.2). A two-way repeated measures ANOVA on the z-scores showed a significant main effect of both blur ($F(2, 38) = 136.007$, $p<0.001$) and test ($F(2,38) = 285.729$, $p<0.001$) as well as a

significant interaction between the two (F(4,76) = 50.704, p<0.001). A comparison of main effects showed the differences lay between the form test and the two motion tests (form mean = 4.940, motion mean = 1.119, biological motion mean = 0.345, p <0.001), with no significant difference between coherent motion and biological motion (p = 0.087). This indicates that blur had a differential effect on coherent form compared to the two motion tests.

3.3.2 SSVEP

3.3.2.1 VEP Topography

Figure 3.3 shows topographic plots of group-level T^2_{circ} values for the F1 and F2 responses to form and motion stimuli. The plots are thresholded at p=0.05 corrected for false discovery rate (Benjamini & Hochberg, 1995), with non-significant values plotted in green (equivalent of T^2_{circ} <3.25). T^2_{circ} values above 5.65 were highly significant (p<0.001).

Motion F1 responses showed peak activation over the occipital midline, while the form stimulus produced a lateralised F1 response. This pattern is consistent with previous findings with these stimuli (Wattam-Bell et al, 2010). Increasing blur led to an overall reduction in activation. This effect was greater for the form stimuli than the motion, with the two highest levels of blur leading to a loss of the lateralised form response. F2 responses, which reflect local processing at least in part, differed somewhat in their spatial patterning compared to F1. F2 activation was localised to the occipital midline for both form and motion at all blur levels. Significant F2 T^2_{circ} was lowest in the 'no-blur' condition for form and motion. Form F2 T^2_{circ} values increased with blur while motion F2 T^2_{circ} values peaked in the 0 cm blur condition.

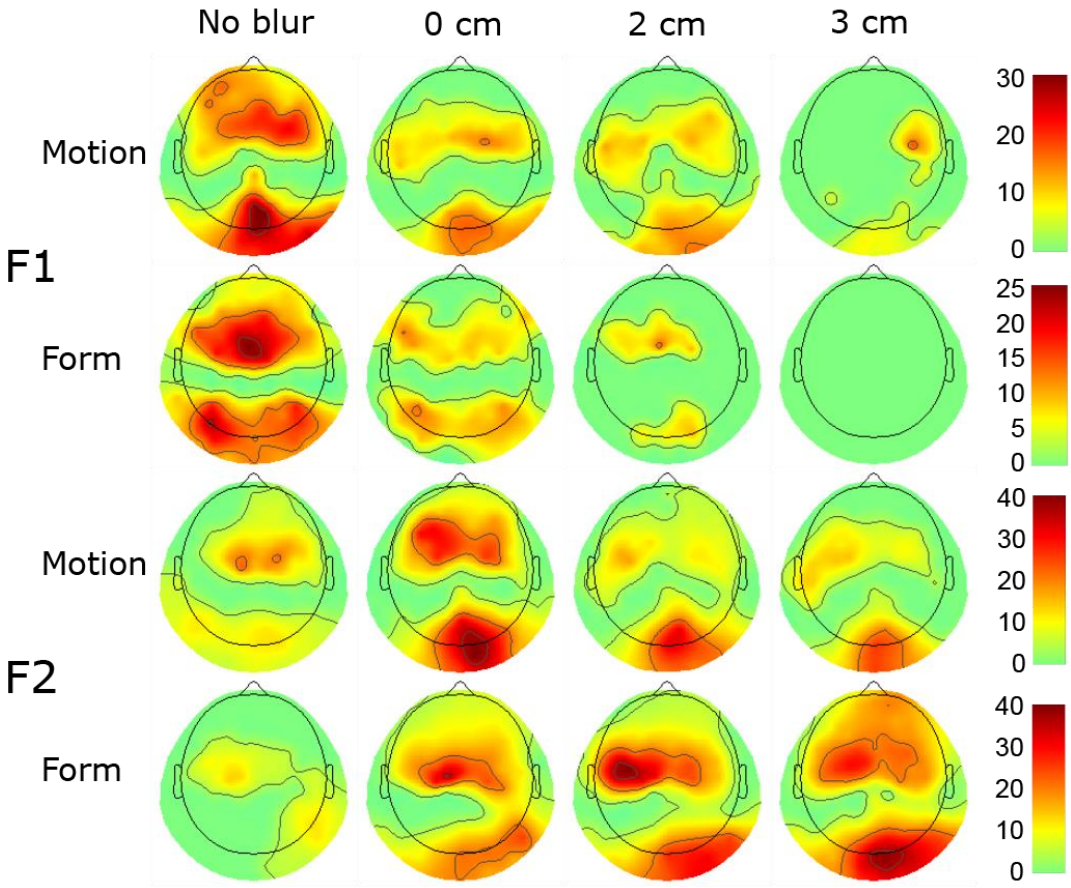

Figure 3.3. Group analysis of motion and form for each level of blur. These maps represent statistically significant T^2_{circ} values across scalp electrodes. These are projected onto a 2-dimensional surface, interpolated onto a Cartesian grid and mapped onto different colours according to the given scales representing the T^2_{circ} value. Areas plotted in green did not produce a significant T^2_{circ} response (p>0.05). T^2_{circ} values above 5.65 were highly significant (p<0.001). Views are given as from the top of the head.

3.3.2.2 VEP Amplitude

Regions of interest (ROIs) were selected for further analysis at both F1 and F2, these are shown above the associated plots in Figure 3.4. The motion F1 ROI was located over the central occipital pole, while the form F1 ROI consisted of two regions located laterally over occipital cortex. The F2 ROI for both motion and form was located over the central occipital pole. ROIs were selected based on the posterior channels showing the highest overall

activation in Wattam-Bell et al (2010). For each ROI, overall amplitude was calculated by vector-averaging the Fourier coefficients across all the channels comprising the ROI, and then taking the absolute value of the average.

Mirroring the results seen in the topographic plots, F1 amplitude decreased in both form and motion ROIs with increasing blur (see Figure 3.4). A repeated measures ANOVA with a Greenhouse-Geisser correction confirmed that amplitudes significantly varied between blur levels (form: $F(2.219, 42.162) = 6.790$, $p = 0.002$; motion: $F(2.203, 41.856) = 7.422$, $p = 0.001$). Plotting F1 amplitudes for both stimuli together using log axes (Figure 3.4) results in two near-parallel curves. This is consistent with an overall lower response to the form stimulus, and with blur acting as a constant multiplicative factor for both stimuli.

There was no overall significant effect of blur on F2 amplitude (form: $F(2.103, 40.479) = 0.321$, $p = 0.741$; motion: $F(2.381, 45.233) = 1.147$, $p = 0.338$).

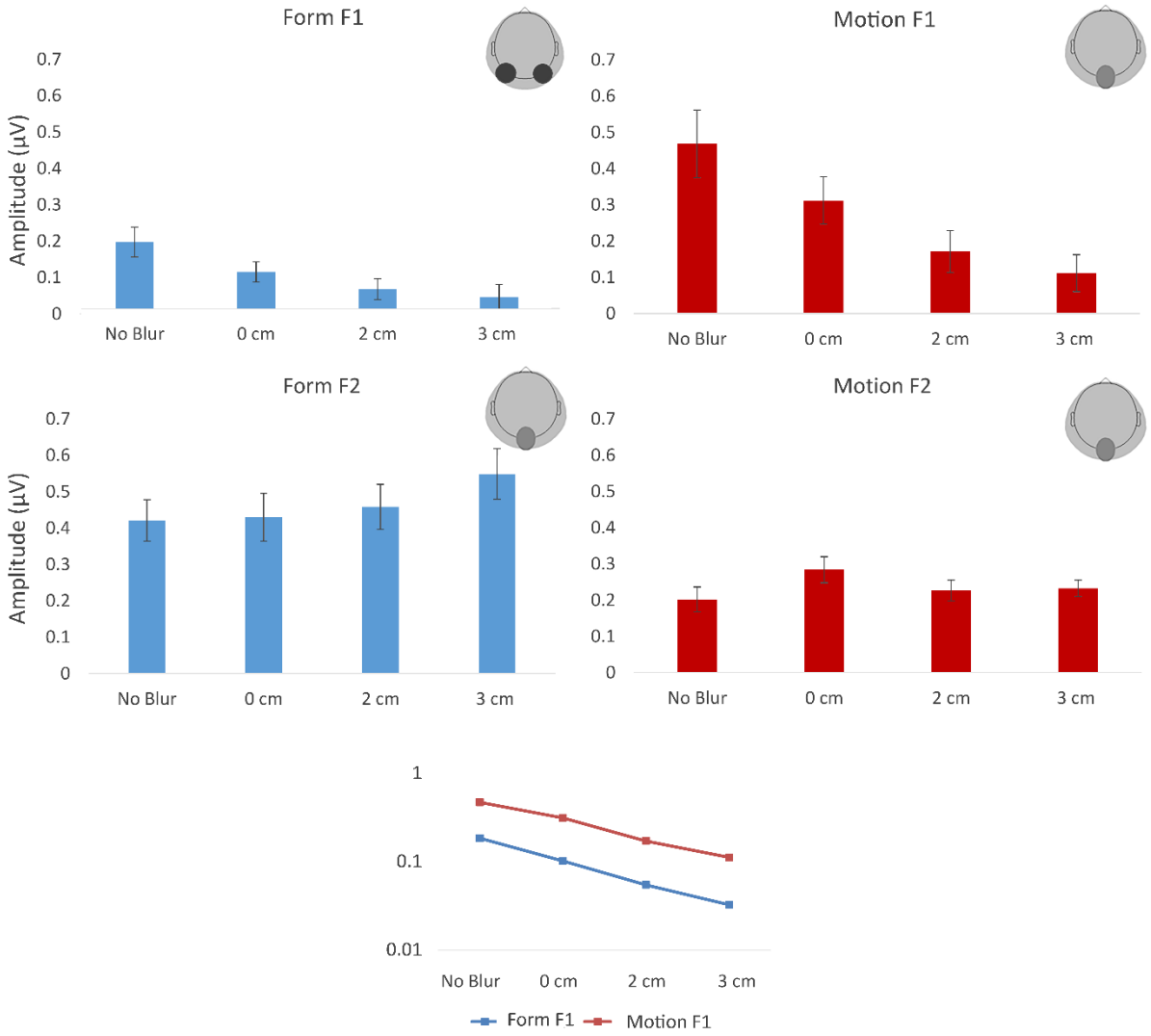

Figure 3.4. Group averaged F1 (top row) and F2 (bottom row) ROI amplitudes (μV) for form and motion. Error bars represent the standard error of the mean.

3.4 DISCUSSION

The results of the study show that blur significantly decreases behavioural responses to coherent form and motion, but not biological motion perception. Cortical responses to coherent form and motion, in the form of VEP amplitudes, were also significantly reduced under blurred conditions.

All three tests showed some elevation of threshold with increasing blur. This indicates that high spatial frequencies contribute in some degree to coherent form, coherent motion and biological motion perception. However, when directly comparing the three tests to one another using Z-scores, coherent form is more adversely affected than either of the motion tests. The loss of coherent form perception at mid and high blur levels indicate that high spatial frequencies are necessary for detecting coherent form in the current stimuli. Motion perception however remained functional albeit impaired, suggesting that high spatial frequencies contribute, but are not essential, for detecting coherent motion in these stimuli. Biological motion remained intact with only very superficial effects on threshold indicating that low spatial frequencies are sufficient for its perception.

The reason for these differences may lie in the pathways which process form, motion and biological motion. Form perception has been argued to be processed predominantly by the ventral stream which receives input from the parvocellular system while motion perception is processed via the dorsal stream, which receives input from the magnocellular system (Livingstone & Hubel, 1988; Merigan & Maunsell, 1993). The parvo- and magnocellular systems differ in their relative contribution from high and low spatial frequencies, with the parvocellular system favouring high and the magnocellular low spatial frequencies. Our results support this view in that form perception was more affected by the loss of high spatial frequencies than motion perception.

The finding that biological motion perception is not significantly affected by blur is in line with previous work by Ahlstrom et al (1998). The pSTS has been identified as a key region involved in the perception of biological motion (Gilaie-Dotan, Kanai, Bahrami, Rees, & Saygin, 2013; Grossman, Battelli, & Pascual-Leone, 2005; Krakowski et al., 2011; Saxe, Xiao, Kovacs, Perrett, & Kanwisher, 2004; Saygin, 2007; Ayse Pinar Saygin, Wilson, Hagler Jr, Bates, & Sereno, 2004) and is known to be a convergence point for the dorsal and ventral streams (Puce & Perrett, 2003). Input from orbitofrontal regions and amygdala also contribute to biological motion perception providing social and emotional context to the motion (Bonda, Petrides, Ostry, & Evans, 1996; Grezes, 1998). These complex interactions between different brain regions may allow effective biological motion perception in conditions where the visual input is reduced. For example, in the absence of high spatial frequencies and therefore potential reductions in ventral stream activation, visual input from the dorsal stream may be sufficient for biological motion perception. This view is supported by a lesion study of an individual lacking the ventral stream. Gilaie-Dotan et al (2011) reported the case of a patient with substantial ventral lesions within the occipital cortex. Despite this the patient had normal biological motion perception and this was correlated with activation in region MT/V5.

The finding of a reduction in F1 amplitude for both form and motion indicates that blur reduces the information used by the visual system in order to detect global organisation within the stimuli. As high spatial frequency information is lost, neurons tuned to higher frequencies will be excluded from the analysis of the image. As a result, the processing of increasingly blurred stimuli is likely to be carried out by increasingly smaller sub-populations of neurons. T^2_{circ} results show that statistically significant form VEP responses are lost at high levels of blur but maintained for motion. This suggests that as blur increased there was reduced processing of coherent form patterns in associated brain regions. The fact that the

motion system receives a greater input from lower spatial frequencies than the form system may explain why some neural activation was recorded even at high levels of blur.

F1 amplitudes were lower for form than for motion, even with no blur. A comparison of these on log axes (Figure 3.4) suggests that blur-related amplitude changes for neural responses in the regions of interest could be explained by blur having similar multiplicative effects for both kinds of stimuli. This would suggest that the form stimulus is distinctive only in having an overall lower neural response. However, this conclusion is at odds with the behavioural findings, in which discrimination thresholds with no blur were closely matched. This discrepancy may be due to a number of factors, including nonlinearities in the mapping from ROI F1 amplitude to behavioural discrimination threshold, and crucially, the fact that VEP measures relate only to the case of 100% coherence, while threshold measures come from low-coherence stimuli. In summary, our behavioural results support the conclusion that sensitivity to coherent form vs motion in these stimuli is differentially affected by blur, while our EEG results suggest that at 100% coherence, differences in amplitudes of cortical responses may be well explained simply by an overall lower response to form.

While loss of information would explain reductions in F1 amplitude with blur, it would also predict reductions in F2 amplitude, related to processing of the local elements in primary visual cortex. Surprisingly, we found that F2 amplitudes were not significantly affected by blur. Since the F2 is a response to the broadband spatio-temporal transients occurring each time the stimulus switches between coherence levels, it is likely to involve magnocellular mechanisms. The magnocellular system's preference for low spatial frequencies could therefore explain why F2 was not strongly affected by removal of high spatial frequencies.

The results found are broadly consistent with the psychophysical data of Zwicker et al (2006). They found global form coherence thresholds worsened rapidly with lenses stronger than +2D and +2.25D. This mirrors our finding as global form thresholds became impaired at

blur levels comparable to those in our 2 and 3 cm condition. Motion results were less affected by blur in Zwicker et al's study, however some decrease was seen at the very highest level of blur tested (+3.5D and +4D). This is similar to our findings in that motion thresholds were less affected than form thresholds by blur but showed some degree of impairment at high levels of blur. The present results are also broadly consistent with the psychophysical data of Braddick et al (2007) on the effect of blur on form and motion coherence thresholds. They only found significant effects on form and motion thresholds with high levels of blur, +7D and +10D lenses respectively, as did the current study in the 2 and 3 cm conditions.

Our results support previous findings into the interaction between spatial frequencies and dot displacement. Cleary and Braddick (1990) found that d_{max}, increased when high spatial frequencies were filtered out of the stimulus. Blur simulating an acuity of 3.56 CPD and below led to progressively higher d_{max} indicating reduced sensitivity. Similar results have been reported by Barton et al (1996) who found reductions in motion coherence thresholds for low dot displacement (<16´) under blur but not for higher dot displacement, concluding that high spatial frequencies are important for motion discrimination within this range. The current study used a dot displacement of 8.6´, falling within the low displacement range. These results have been attributed to multiple motion processing channels selective for specific spatial frequencies. At high dot displacements, high spatial frequency channels exceed their d_{max} and as a result begin to mask low spatial frequency channels. When these high spatial frequencies channels are excluded, the masking does not occur, allowing low spatial frequency channels to function efficiently (Cleary & Braddick, 1990). This suggests that with larger dot displacements, thresholds may begin to improve with increasing blur in the current study.

While stimuli were matched across the VEP and behavioural tests, the location of the stimuli on the display was not the same across the two tests. VEPs were presented centrally, while

behavioural tests were presented to the left of right of fixation. Because the coherent pattern subtended 16°, when either the centre was fixated (VEP) or a region near the edge was fixated (behaviour), some of the stimulus was in the periphery. However, in behavioural tests a greater proportion of the coherent stimulus was in the periphery. This difference might be expected to bias the behavioural measure to show a greater relative advantage for motion vs form than the VEP measure. Consistent with this, the behavioural but not the VEP measure shows a motion advantage that could not be explained by a mis-match in initial (unblurred) response. However, conclusions from direct comparisons of VEP and behavioural measures are also limited because all VEP measures were at 100% coherence.

The differences between form and motion perception observed in the current study diverge from what is seen in both developmental and clinical populations. Our study found form perception was more impaired by blur than motion perception. In clinical populations it is overwhelmingly motion perception which shows the greater impairment, indicating a selective vulnerability of the dorsal stream (Atkinson et al., 1997; Atkinson et al., 2003; Braddick et al., 2003; Gunn et al., 2002; Spencer et al., 2000). This suggests that factors other than acuity are the key to constraining form and motion coherence thresholds in development. The findings on biological motion perception however are in line with those reported in visually impaired populations (Hadad, Maurer, & Lewis, 2012) and these results together suggest that biological motion perception may be highly robust against loss of high spatial frequency information.

The results suggest that when working with developmental and low vision groups, coherent form and motion sensitivity are unlikely to be directly influenced by acuity and contrast sensitivity, unless acuity is reduced significantly (<1 LogMAR). In chapters 4 and 5 of this thesis coherent form, motion and biological motion perception are assessed in patients with cone disorders. Based on these results alone it would be expected that patients may demonstrate reduced form perception relative to motion and a potential sparing of biological

motion perception. However, there are number of issues to consider with cone disorder patients.

Cone disorder patients' vision is restricted to rod photoreceptors which is likely to have additional effects on the perception of coherent form, motion and biological motion. Rods, for example, demonstrate reduced temporal resolution which may well impact on motion perception. To address this, the next chapter (chapter 4) describes testing of controls with normal vision on coherent form, motion and biological motion perception under a range of light levels aimed to stimulate cones and/or rods. In addition to the limitations of rod vision in cone disorder patients there is also the possibility that their vision will have changed and adapted over time to optimise the visual input they receive. Chapter 5 and 6 therefore compares form, motion and biological motion perception of cone disorder patients to controls on behavioural (chapter 5) and VEP (chapter 6) tests.

Chapter 4. CORTICAL PROCESSING OF COHERENT FORM, COHERENT MOTION AND BIOLOGICAL MOTION UNDER LOW LIGHT LEVELS

4.1 INTRODUCTION

The current study investigates the impact of low light conditions on coherent form, motion and biological motion perception in people with normal vision. This was achieved using a combination of behavioural psychophysics and steady-state VEP under light intensities ranging from photopic to scotopic levels.

The study aimed to understand the contribution of rods and cones to coherent form, coherent motion and biological motion perception. Gaining an understanding of visual function in observers with healthy vision under light conditions designed to activate rods and/or cones will provide important baseline information for comparison with cone disorder patients in later chapters (chapters 5&6).

Previous research into visual perception under low light has generally studied early-level visual processing including detection of local motion, visual acuity, stereopsis, flicker fusion and spectral sensitivity (Barlow, 1962; Cavonius & Robbins, 1973; Kellnhofer, Ritschel, Vangorp, Myszkowski, & Seidel, 2014; Kinney, 1958; Livingstone & Hubel, 1994; Mandelbaum & Sloan, 1947; Nygaard & Frumkes, 1985; Riggs, 1965; Teller, 2009; Westheimer, 1965). Research exists into reading under scotopic conditions (Chaparro & Young, 1989, 1993), however research into mid- and high-level vision is relatively sparse.

While our study is primarily concerned with the impact of scotopic and mesopic conditions on mid- and high-level vision, it is also important to consider how far these effects may result from the impact of these conditions on the processing of lower-level mechanisms. Area V1 performs local processing of visual signals, which go on to be integrated for global form and

motion processing. Duffy & Hubel (2007) looked at basic receptive field properties of V1 neurons in macaques, including directional selectivity and orientation selectivity, and found that these were maintained in scotopic conditions. This has implications for both coherent motion and form perception as it suggests that at the local level, perception should be unimpaired. However, other properties of scotopic vision may impact on early visual perception which in turn may affect global processing. For example, visual acuity is known to be reduced in scotopic conditions due to the poor spatial resolution of the rod system. Maximum scotopic acuity is ~0.7 LogMAR as opposed to -0.2 LogMAR in photopic conditions (Riggs, 1965). Reduced acuity may lead to reduced sensitivity to local cues necessary for later integration into global constructs. Chapter 3 investigated the effects of reduced acuity and contrast sensitivity on global form and motion processing. Scotopic vision also has relatively sluggish temporal properties, at least in central areas of the visual field, which may have an impact on motion processing (Conner, 1982; Takeuchi & De Valois, 2000).

Studies into coherent motion perception under low light have found it to be generally preserved (Billino, Bremmer, & Gegenfurtner, 2008; Grossman & Blake, 1999). Grossman & Blake (1999) examined coherent motion thresholds under low light using random dot kinematograms (RDK). Translational coherent motion moving at 3.2 deg/sec was presented to participants in a 2-interval forced choice task under photopic and scotopic conditions and participants were required to indicate the presence of coherent motion. They reported that coherence thresholds were the same under low light as photopic conditions. Billino et al (2008) tested detection of translational coherent motion under three light intensities using RDKs. They found that detection thresholds became progressively worse as luminance fell from 98.5 to 0.285 and 0.018 cd/m^2.

Biological motion perception was also investigated in these two studies. Billino et al (2008), reported a U-shaped result with best performance in photopic conditions, worst performance

at mesopic light levels (0.285 cd/m^2) and scotopic performance, at 0.018cd/m^2, falling between the two. In contrast, Grossman & Blake (1999) found biological motion detection to deteriorate in low light. However, they only tested under the two light levels 3.6 and 0.036 cd/m^2. Testing in darker conditions might have resulted in the U-shaped performance described by Billino et al (2008).

Steady-state Visual Evoked Potentials (SSVEPs) have not previously been used to study scotopic form and motion perception. However, they have been used in the study of coherent form and motion development (Hou, Gilmore, Pettet, & Norcia, 2009; Norcia et al., 2005; Palomares, Pettet, Vildavski, Hou, & Norcia, 2009; Wattam-Bell et al., 2010; Weinstein et al., 2012). For example, Wattam-Bell et al. (2010) found distinct difference between infant and adult global form and motion SSVEP topographies. It remains unclear how much these differences reflect immaturities in extra-striate regions, or are a result of lower-level limitations of spatial vision in infancy. Testing under low light conditions will therefore also provide further insight into how coherent form and motion topography is affected when spatial visual input is reduced.

The current study aimed to build on and extend previous research into visual perception in low light. The light conditions extended over a wider range than those previously used (Billino et al, 2008; Grossman & Blake, 1999) to test vision well into the scotopic range. To obtain a fuller picture of extra-striate processing, we tested perception of coherent form as well as of coherent motion and biological motion. As well as behavioural tests of sensitivity, steady-state EEG measures were used to investigate changes in the amplitudes and cortical distributions of neural responses underlying coherent form, coherent motion and biological motion perception under different light levels. Results from this study will provide important baseline information for comparison with data from cone disorder patients (chapters 5&6).

4.2 METHODS

4.2.1 Participants

Twenty normally sighted participants (mean age 25.2 years, standard deviation 4.6) completed the experiment within the Faculty of Brain Sciences, Division of Psychology and Language Sciences, University College London. Information sheets were given and Informed consent was obtained before testing commenced.

4.2.2 Tests Completed

For the behavioural tests participants completed coherent form, coherent motion, biological motion and contrast sensitivity tests. For the SSVEP tests participants completed coherent form and coherent motion tests.

Details of the stimulus design, task procedure and SSVEP data handling can all be found in the General Methods (chapter 2). All tasks were carried out as described there with additional features described below.

4.2.3 Light Levels

Four light levels were used in the experiment. This was done in order to assess the relative contribution of rods and cones to perceptual sensitivity and cortical EEG responses. Light levels were achieved using sheets of characterised neutral density filters (Sabre International Ltd, UK) which were placed over the display monitor. There was no other light source in the room besides the display screen.

The four luminance levels were classified as photopic (8.7 cd/m^2), high mesopic (0.8 cd/m^2), low mesopic ($2.7x10^{-2}$ cd/m^2) and scotopic ($8.7x10^{-4}$ cd/m^2). The values here refer to the

luminance of the dots/lines making up the stimuli; these were presented against a black background with a 3.24 Log Weber Contrast (LogWC) for each light level. Behavioural tests were completed under the four light conditions while EEG tests were completed under the high mesopic and scotopic conditions. Testing at all four light levels for the EEG would have required a lengthy test period which would have impacted on the quality of the data. The high mesopic and scotopic conditions were selected in order to provide an informative spread of luminance levels.

Participants were dark adapted prior to testing (see “Experimental design and procedure” section below for further details). However, tests were completed with a natural pupil so that the precise retinal illuminance for each condition varied between participants. To address how large this variation was and to check that retinal illuminance fell within photopic, mesopic and scotopic conditions, a subset of participants (N = 5) had their retinal illuminance levels calculated, based on their pupil size under each condition. Pupil size was measured by taking an image of the pupil whilst viewing the form stimuli at 60 cm. Images were captured with an infrared camera and pupil diameter was calculated using image processing software. At retinal illuminance levels above 3 log scotopic trolands (logSTr), rods become saturated and cones take over, while the mesopic range is defined as falling between -1 and 2 logSTr (Stockman & Sharpe, 2006). Mean illuminance levels are shown in Table 4.1, confirming that on average participants were viewing the stimuli in the desired luminance ranges and that individual pupillary variations were minor. Individual pupil size and illuminance levels are given in appendix VI.

	Mean (SD) Retinal illuminance, log STr
Photopic	3.21, (0.08)
High Mesopic	1.71, (0.08)
Low Mesopic	0.30, (0.08)
Scotopic	-1.15, (0.06)

Table 4.1. Mean and standard deviation of retinal illuminance level (log STr) for each light level, for the sample of participants whose pupil sizes were measured.

4.2.4 Experimental Design and Procedure

Testing was completed in a dark environment with no stray light. All windows and light sources were sealed during the experiment using black-out curtains and tape.

Participants were dark adapted before the tests. For the photopic condition participants were seated in a dim room for 10 minutes before testing began, while for the two mesopic and the scotopic conditions participants were given blackout goggles (MindFold, Inc) to wear for 30 minutes. Light levels were counterbalanced so that half of participants completed the mesopic level, followed by scotopic, while half completed the scotopic level followed by mesopic. The photopic level was always completed either at the beginning or end of testing (see Table 4.2).

	Condition				Participants
Order 1	Photopic	H. Mesopic	L. Mesopic	Scotopic	N=5
Order 2	H. Mesopic	L. Mesopic	Scotopic	Photopic	N=5
Order 3	Photopic	Scotopic	L. Mesopic	H. Mesopic	N=5
Order 4	Scotopic	L.Mesopic	H. Mesopic	Photopic	N=5

Table 4.2. The 4 condition orders that were used for behavioural tests.

Participants began with a practice session, which included all behavioural tests, completed in the photopic light level. The practice involved three runs of the form, motion and biological motion tests, with each run containing 30 trials. Participants also completed one run of the contrast sensitivity test which contained 100 trials. Thresholds across the form, motion and biological motion tests were compared to assess the consistency of each participant's performance. This comparison showed that most participants (18 out of 20) maintained consistent thresholds after three runs. Those who did not do so were given two more runs of the test after which their thresholds were found to be consistent.

For the main experiment, participants completed three runs each of the form, motion and biological tests in each light condition. Each run contained 30 trials. Participants also completed one run of the contrast sensitivity test in each light condition, containing 100 trials. SSVEP testing was carried out after the behavioural tests at the high mesopic and scotopic light levels.

4.3 RESULTS

4.3.1 Behavioural

4.3.1.1 Form, Motion and Biological Motion

The Shapiro-Wilk test was carried out on all behavioural data to assess whether it was normally distributed (Table 4.3). This revealed some data did not fit a normal distribution and as such all data was log transformed before analyses were carried out.

		Original	**Transformed**
Photopic	form	0.49	0.24
	motion	**0.01***	0.17
	bmotion	**<0.01****	0.07
H.Mesopic	form	0.30	0.91
	motion	0.08	0.76
	bmotion	**<0.01****	0.60
L.Mesopic	form	**0.04***	0.07
	motion	**<0.001****	0.07
	bmotion	**<0.001****	0.66
Scotopic	form	**0.01***	0.27
	motion	**<0.001****	0.25
	bmotion	**0.01***	0.12

*Table 4.3. p-values from the Shapiro-Wilk test of normality. Values are given for group results of each test in each light condition, in original data and log-transformed data. P-values <0.05 (shown in bold *) and <0.001 (shown in bold **) indicate that the distribution departs significantly from the normal.*

Thresholds were averaged across three runs per participant and then across the 20 participants. Group averages for each test and light level can be seen in Figure 4.1.

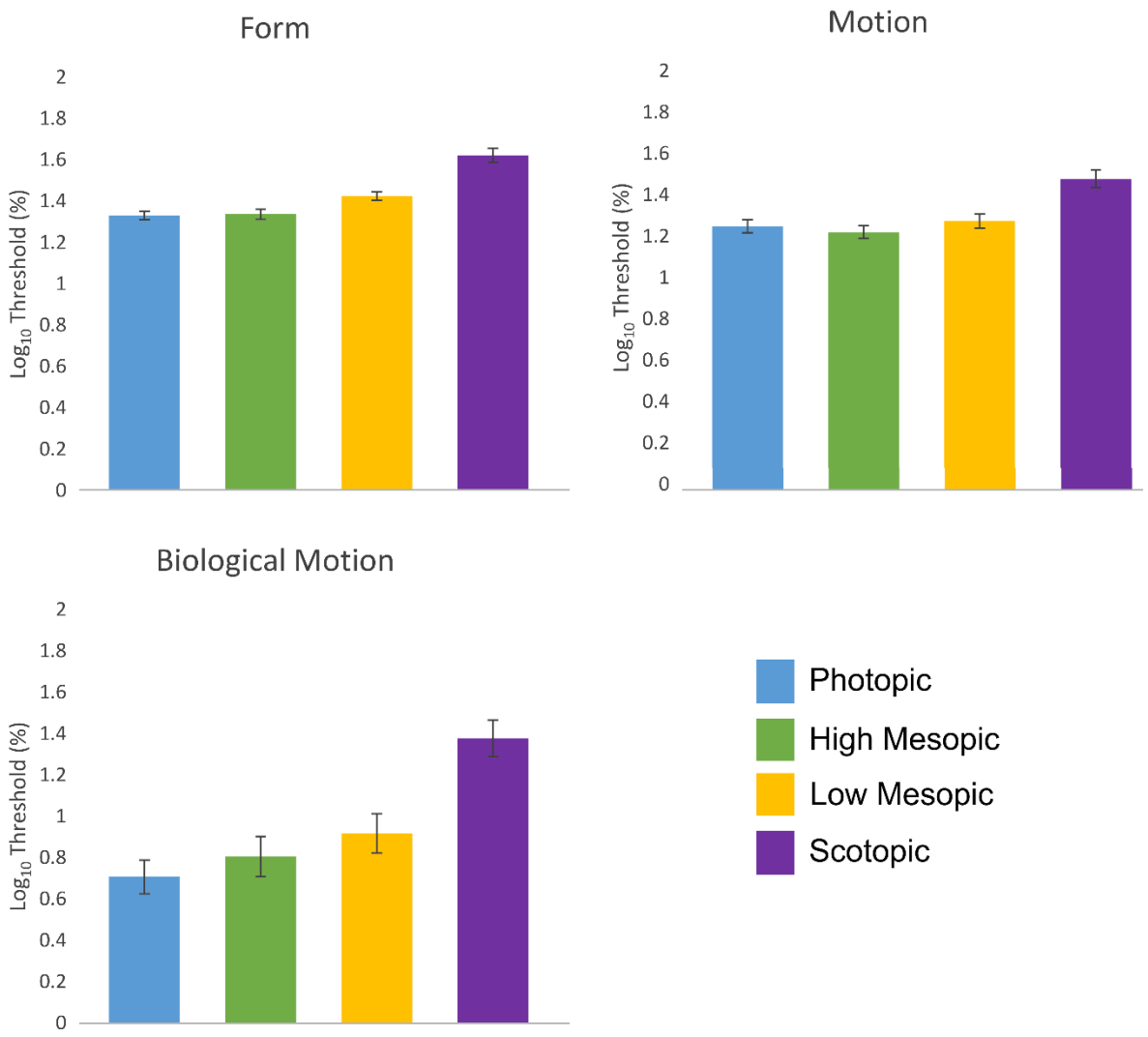

Figure 4.1. Mean thresholds for form, motion and biological motion tests under 4 light levels. Error bars represent the standard error of the mean.

As Figure 4.1 shows, performance on all tests showed a progressive worsening as luminance decreased. Thresholds remained relatively stable across the photopic and high mesopic ranges. However, performance on all form and motion tests began to decline in the low mesopic range, leading to a sharp decline in the scotopic range, between 0.027 and 0.00087 cd/m^2 on all three tests.

Repeated-measures ANOVAs revealed main effects of light level on all three tests (Form: $F(3,57) = 54.769$, $p<0.001$; Motion: $F(3,57) = 46.587$, $p<0.001$; Biological Motion: $F(3,57) = 31.334$, $p=0.001$).

In order to compare the tests to one another, z-scores with respect to photopic performance were calculated. These normalised the results so that 0 represents the photopic result for all three tests. Z-score results are shown in Figure 4.2 and demonstrate greater impairment with decreasing luminance for coherent form thresholds than for coherent motion or biological motion. A repeated measures ANOVA of the z-scores found a significant main effect of both luminance ($F(2,38) = 111.032$, $p<0.001$) and test ($F(2,38) = 7.176$, $p<0.002$) as well as a significant interaction between the two ($F(4,76) = 8.099$, $p<0.001$). Post hoc comparisons using Bonferroni corrections revealed that the main effect of test type was driven by differences between the form result (mean = 1.396, sd = 1.05) and the other two tests (Motion: mean = 0.518, sd = 1.06, Biological Motion: mean = 0.898, sd = 1.04).

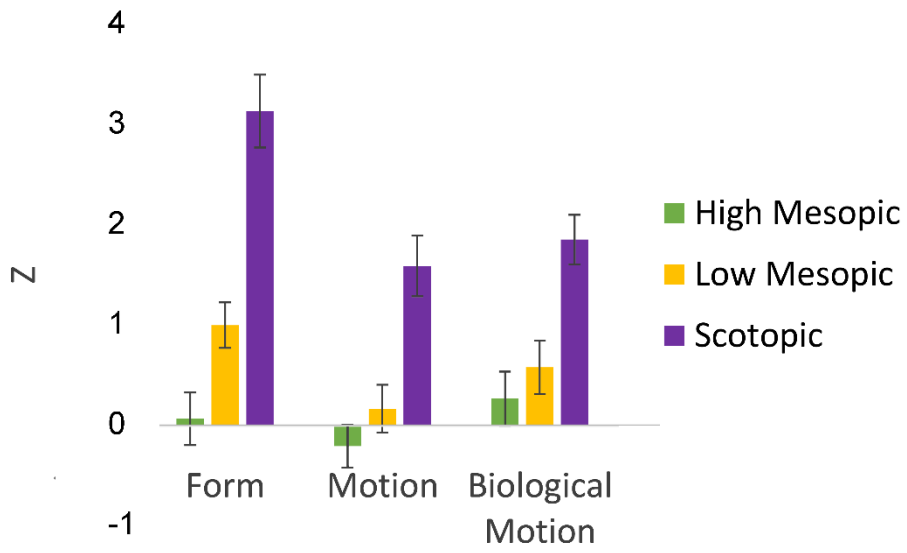

Figure 4.2. Mean z-scores for form, motion and biological motion thresholds. Positive z-scores represent higher coherence thresholds and therefore worse test performance. Error bars represent the standard error of the mean.

4.3.2 SSVEP

4.3.2.1 VEP Topography

Figure 4.3 shows topographic plots of group-level T^2_{circ} values (a statistical measure of signal-to-noise ratio) for the F1 and F2 responses to form and motion. The plots are thresholded at p=0.05 corrected for false discovery rate (Benjamini & Hochberg, 1995), with non-significant values plotted in green.

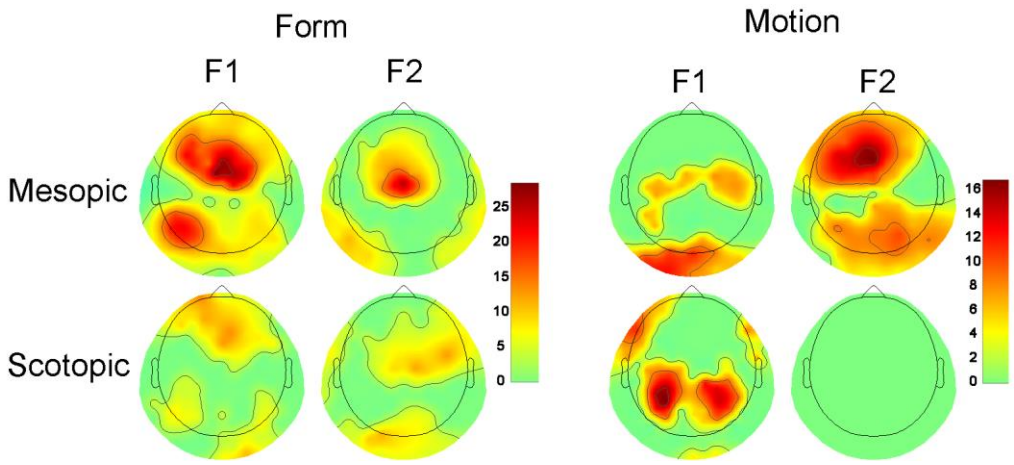

Figure 4.3. T^2_{circ} topographic plots of global form and motion activation. F1 activation relates to responses to the global structure of the stimulus while F2 activation relates to local changes in the stimulus display.

In the mesopic condition, motion F1 responses showed peak activation over the occipital midline, while the form stimulus produced a lateral F1 response, predominantly in the left hemisphere. This pattern is consistent with previous findings with these stimuli at photopic levels (Wattam-Bell et al, 2010).

The scotopic condition shows a reduced F1 T^2_{circ} value for form but not for the motion response. Form activation remained lateral, albeit reduced, however motion activation showed a shift from an occipital midline response to a lateral response.

At the scotopic light level, F2 responses, which reflect local processing, were localised to the occipital midline for form and motion. Motion F2 responses were reduced to an overall non-significant level.

To compare the F1 topographies, the posterior electrodes were divided into five distinct regions, as described in Wattam-Bell et al (2010), and our signal-to-noise measure (T^2_{circ}) was averaged across the 8 electrodes within each region. This gave 5 mean T^2_{circ} values for form and motion. Figure 4.4 shows mean signal-to-noise (T^2_{circ}) across these five regions in mesopic and scotopic conditions. Form responses reduced in the scotopic condition but showed a broadly similar pattern of response across the five regions. Motion responses remained consistently strong in scotopic compared to mesopic conditions, but the pattern of activation changed from a central response mesopically to a more lateral response scotopically.

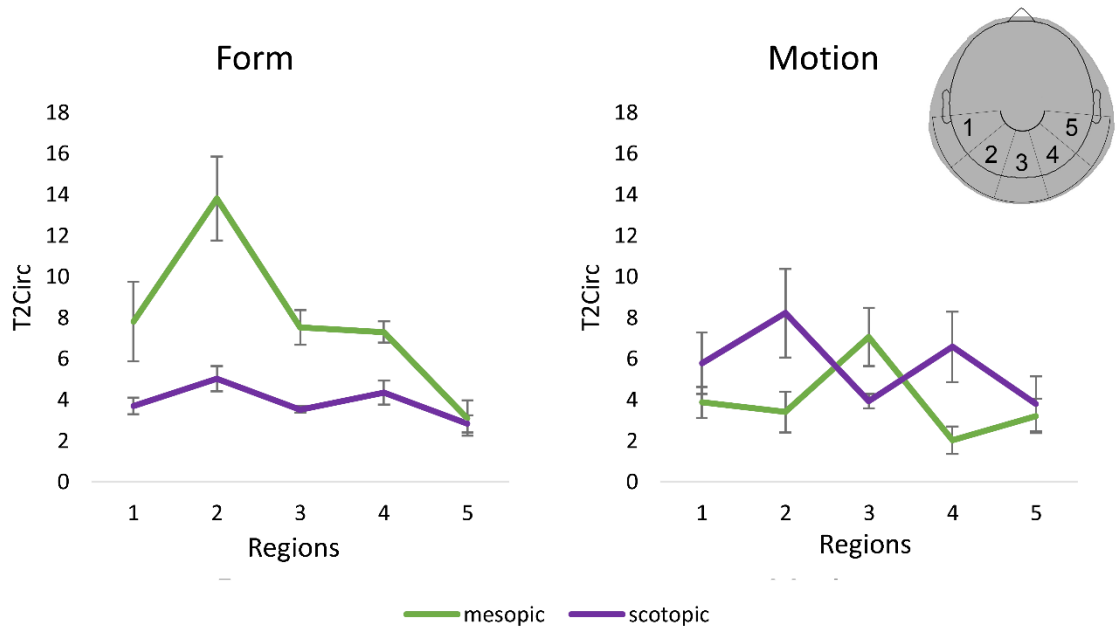

Figure 4.4. Mean mesopic and scotopic T^2_{circ} values for the form and motion tests across five regions of the scalp. Error bars represent the standard error of the mean.

A repeated measures test x light x region ANOVA found a main effect of test ($F(1,7) = 5.732$, $p = 0.048$), light ($F(1,7) = 55.187$, $p<0.001$) and region ($F(4,28) = 14.075$, $p <0.001$). There were also significant interactions between test*region ($F(4,28) = 4.404$, $p = 0.007$), light*region ($F(4,28) = 6.029$, $p=0.001$) and test*light*region ($F(4,28) = 3.571$, $p =0.018$), indicating that responses to the two tests differed across light conditions and across the cortical surface.

4.3.3 Contrast Sensitivity Functions

Group average CSF plots are shown in Figure 4.5. The qCSF method (Lesmes et al., 2010) calculated four parameters of the CSF and these were used to plot the function. The solid line represents the group average contrast sensitivity as calculated for each light level. The shaded region around the line represents the 95% confidence interval for the group average. Contrast sensitivity reduced as a function of luminance. Decreased light levels led to participants having a lower visual acuity, as demonstrated by the reduced cut-off spatial frequency (the estimated CPD at which sensitivity is 0), and reduced peak contrast sensitivity.

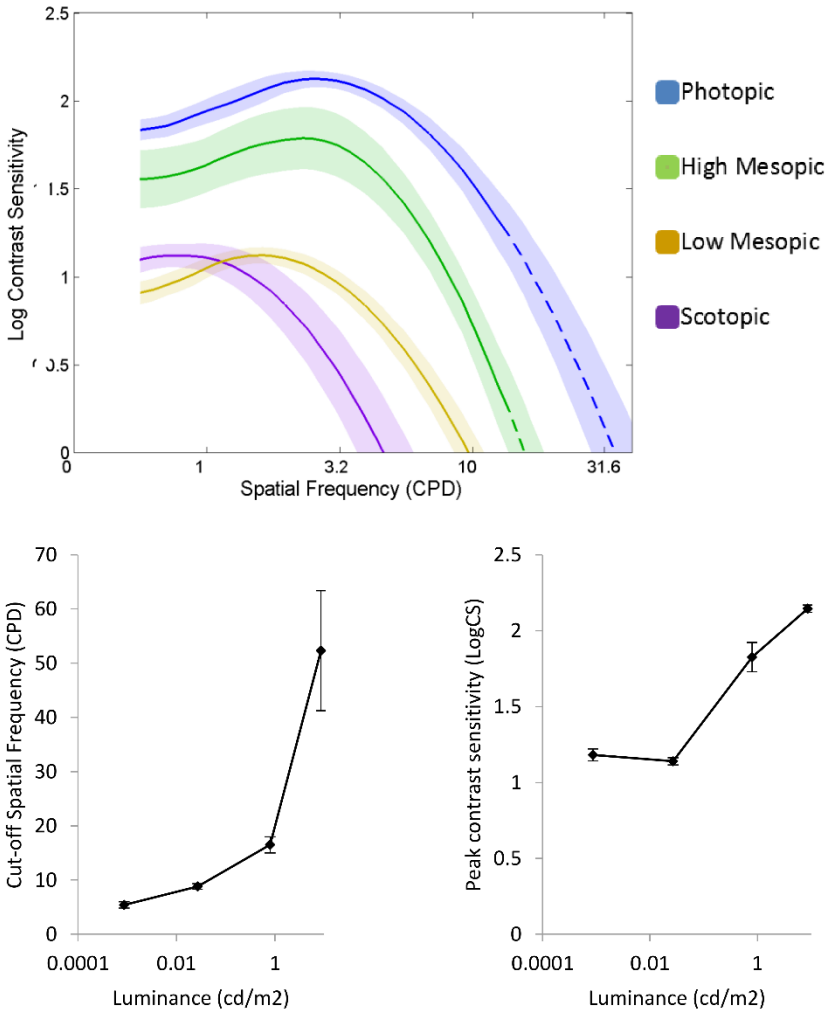

Figure 4.5. CSF for each light level (top) and cut-off SF and peak CS across light condition (bottom), error bars represent the standard error of the mean. Solid lines of the CSF represents the group average, shaded regions represent the 95% confidence interval around the mean. In the two brightest conditions participants could detect the highest spatial frequency available from the display, portions of fitted CSF curves above this frequency (13.75 CPD) are shown by the dotted lines.

Within the photopic and high mesopic condition there were ceiling effects in all participants due to limitations of the display monitor and testing distance. The maximum spatial frequency that could be displayed was 1.14 LogCPD = 13.75 CPD, an acuity which all

participants exceeded at photopic and high mesopic levels. Data above this value are represented with a dotted line and were derived from the fitted CSF.

Two variables were calculated from the CSF – the cut-off spatial frequency (cut-off SF) and the peak contrast sensitivity (peak CS). Figure 4.5 shows the mean cut-off SF and peak CS across participants for each light level. Reducing luminance significantly reduced the cut-off SF ($F(1.025,16.392) = 13.37$, $p<0.001$) and peak CS ($F(3, 48) = 87.079$, $p<0.001$).

As expected, the light level manipulations affected basic spatial sensitivity as indexed by the CSF (Figures 4.5), which could potentially contribute to effects on global form and motion perception. To test the extent to which reductions in global form and motion thresholds under low light could be explained by reductions in contrast sensitivity and acuity alone, results were compared to data collected previously in 20 typically sighted participants with simulated low vision (chapter 3). These participants completed the same coherent form and motion tests used here, viewed through a diffuser acting as a low pass filter at different separations from the screen which introduced different levels of blur. All testing was carried out under photopic conditions with an average screen luminance of 30.5 cd/m^2. This luminance was higher than the photopic luminance used here, since the latter was set to a low level to be comfortable in future use with patients with cone dysfunction.

Figure 4.6 shows the effects on the CSF of the four blur conditions (chapter 3) and the four different luminance levels employed in the present experiment. The blur effects approximately span the reductions of cut-off SF and peak CS produced by luminance reduction, although blur introduces greater reduction of contrast sensitivity and somewhat less reduction in cut-off SF than the low mesopic and scotopic luminance levels. Blur levels were selected which matched most closely the effects of photopic, low mesopic and scotopic conditions: for these, the area under the log contrast sensitivity function (AULCSF) is comparable, as shown in the lower right panel of Figure 4.7.

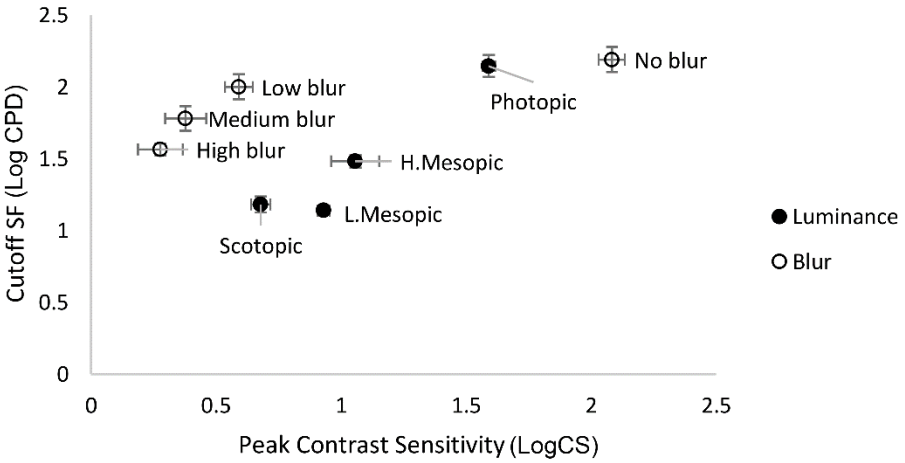

Figure 4.6. Comparison of CSF results previously achieved with varying blur (chapter 3) compared to CSF results achieved here with varying luminance. Mean cut-off SF is plotted against mean peak CS. Error bars represent the standard error of the mean.

Figure 4.7 shows a comparison of form and motion thresholds under blur and luminance conditions which produced comparable effects on CSFs. The differences in global motion and in biological coherence thresholds are relatively small, while for global form thresholds, the blur manipulation produces much stronger effects than the luminance manipulation. These results indicate that the balance of effects produced by low luminance is very different from those predicted on the basis of changes in low-level spatial sensitivity: low luminance has a relatively small effect on form thresholds, and blur a large effect compared to their relative effects on motion thresholds.

Form thresholds were significantly worse under blur than in low light ($F(1,19) = 216.463$, $p < 0.001$). This suggests that form perception under low light is better than would be expected given the reduction in spatial vision. Motion thresholds and biological motion thresholds were not significantly different between blur and luminance conditions (Motion: $F(1,19) = 3.746$, $P = 0.068$; biological motion: $F(1,19) = 1.999$, $p = 0.174$). There were also significant interactions between the blur/ light condition and the three levels tested for form and biological motion results (form: $F(2,38) = 123.076$, $p<0.001$; biological motion: $F(2,38) =$

10.132, p <0.001) but not for motion (F(2,38) = 134.236, p = 0.079). Biological motion results were comparatively worse under scotopic conditions than under blur, while form were better.

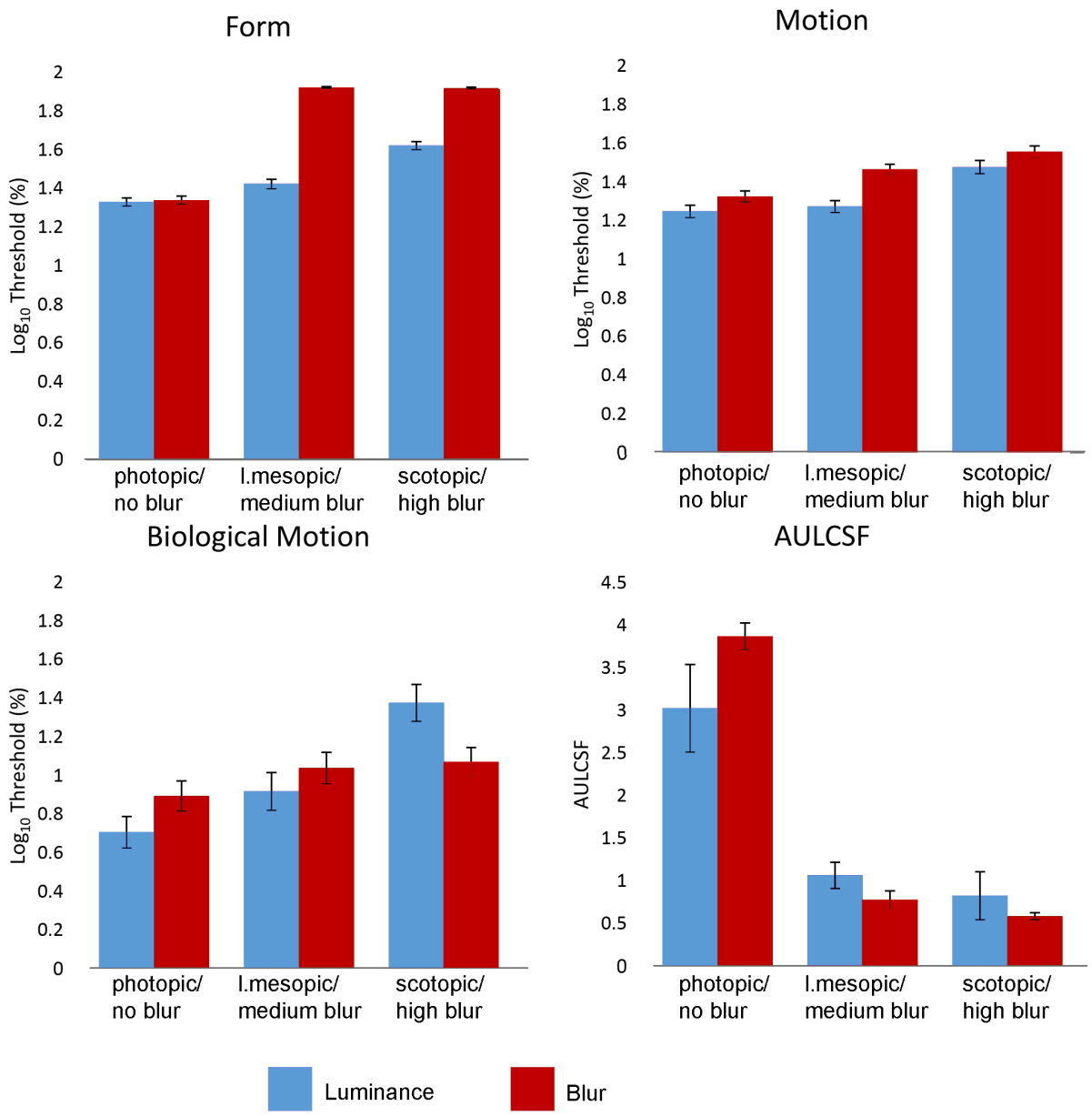

Figure 4.7. Comparison of form, motion and biological motion thresholds attained in the photopic, low mesopic and scotopic conditions to those attained with no blur, medium blur and high blur (described in chapter 3). AULCSF results were matched and are shown.

4.4 DISCUSSION

The current study aimed to understand how mid- and high-level vision is affected by changes in luminance in those with normal vision. Coherent form, motion and biological motion were examined using both behavioural and SSVEP techniques to address how cortical processing of these stimuli varies as luminance decreases. These results will provide control data with which to compare cone disorder patients in future chapters (chapters 5&6).

Coherence thresholds for all three stimuli increased with decreasing luminance, indicating a worsening of performance. However, coherent form perception fared worse than either coherent motion or biological motion perception, indicating that motion perception is relatively less affected by low light. VEP measures showed reductions in cortical response (i.e., in our measure of signal-to-noise) from mesopic to scotopic viewing, paralleling the reduction in behavioural discrimination ability. The transition from mesopic to scotopic conditions also led to some reorganization of topography, particularly for motion responses. These shifts in topography (Figure 4.4) may correspond to changes in cortical visual processing leading to relatively spared motion processing under low light.

Participants' CSF results demonstrated reductions in both contrast sensitivity and spatial acuity as luminance decreased. These results were in line with previous findings on scotopic contrast sensitivity (Barten, 1999). However, the effects on global form, motion and biological motion perception were not uniform, suggesting that spatial limitations of scotopic vision are insufficient in explaining mid-and higher-level visual performance under low light. Comparing the results to data previously collected photopically but with stimuli which were blurred in order to reduce the available spatial information, (chapter 2), scotopic form perception was less impaired than by blur leading to similar overall reductions in spatial vision. This suggests that the level of sensitivity in low light is greater than expected given the spatial impairments. The reason behind this may be that despite matching the blur and

luminance conditions based on AULCSF, blur produced a relatively greater loss of contrast sensitivity than low light. It is therefore possible that form perception is more dependent on contrast than acuity at mid spatial frequencies.

The effect of luminance on global form perception had not been studied previously. On behavioural tests, form perception revealed a greater impairment than global or biological motion. Coherent form perception is processed via region V4 of the extra-striate cortex which receives both parvocellular and magnocellular input (Ferrera, Nealey, & Maunsell, 1994). Parvocellular input is greatly reduced in scotopic conditions (Benedek, Benedek, Kéri, Letoha, & Janáky, 2003; Hassler, 1966) and this loss of input to V4 may be contributing impairments in form perception. This is in contrast to magnocellular input which remains largely intact under low light and could therefore be acting to maintain motion perception. Further work with stimuli specifically designed to isolate magnocellular and parvocellular pathways could provide more insight into their relative contribution to form and motion processing under different light levels.

VEP responses to form and motion show distinct topographical organisation. The results from the mesopic condition show midline occipital motion responses vs. lateral form responses. These regions of activation match those found by Wattam-Bell et al (2010) who used the same stimuli and setup. The different patterns of activation for form and motion support the view that these responses are distinct from one another.

Wattam-Bell et al (2010) found a similar shift in topography to those observed in our study when comparing adult and infant form and motion VEPs. Motion VEP responses shifted from a lateral response in infants to a midline response in adults. This was attributed to reduced inhibitory feedback mechanisms in the infant visual cortex (Wattam-Bell, Corbett, & Chelliah, 2013). Wattam-Bell et al (2013) suggested that midline motion VEP responses reflect inhibitory feedback to V1 from extra-striate regions, with V1 inhibition playing less of a role in

global form perception. The lack of inhibitory feedback seen in the infant cortex is thought to reflect immaturities in cortical development. However, our similar pattern of results indicates that reduced spatial information input to cortical motion mechanisms may have a similar effect. Further source localisation and the use of neuroimaging methods with greater spatial resolution would be needed to confirm the suggestion of a change in the network contributing to the VEP.

Biological motion perception was more impaired scotopically than under blur conditions. This may reflect the importance of precise temporal information for biological motion perception. The sluggish nature of the rod system reduces the accuracy of temporal information reaching the visual cortex (Conner, 1982; Takeuchi & De Valois, 2000). Reduced accuracy will in turn make it harder to extract structural information, leading to a reduced ability to differentiate scrambled from unscrambled biological motion.

Global motion perception was less impaired than global form under low light. However, we did find overall reductions in global motion sensitivity and VEP amplitude in low light. This is in contrast to previous studies which have found, coherent motion perception to be largely unaffected by luminance (Billino et al., 2008; Grossman & Blake, 1999).The differences in results are not explained by the light intensities used as our study found impairments from 0.027 cd/m^2 while Billino et al (2008) did not find impairments in their dimmest condition of 0.018 cd/m^2.

One possible reason for the discrepancy, however, could be the speed of the stimuli. Scotopic conditions have their greatest impact at high spatial frequencies. Takeuchi and de Valois (2000) found velocity discrimination of high temporal frequency drifting sine-wave gratings fell as luminance was decreased. Low temporal frequency discrimination, however, was unaffected. Our study used dots moving at 8.6 deg/sec, faster than those tested by both Billino et al (2008) and Grossman and Blake (1999) and this may explain why performance

fell in our study. Indeed, when Billino et al (2008) tested participants with faster coherent motion (6.6 deg/sec and 13.2 deg/sec) sensitivity did begin to reduce in low light in line with our findings. In contrast Orban et al (1984) have reported low temporal frequencies to show the greatest impairment in low light relative to intermediate temporal frequencies. Testing at lower speeds than those described here may therefore lead to further reductions in scotopic global motion sensitivity.

Previously, Billino et al (2008) reported a U-shape effect of luminance on biological motion perception with performance worst in mesopic conditions relative to scotopic and photopic conditions. Our results did not find this pattern. Instead, luminance had a monotonic effect on performance with scotopic light causing the most impairment. Billino et al (2008) argued that interactions between rods and cones in mesopic conditions can lead to disruptions in spatio-temporal processing of the motion. If this was the case our results should have followed the same pattern. However, our participants showed very little change in biological motion thresholds across the photopic and mesopic light levels. Our results therefore suggest that the cone input seen at these light levels aids biological motion detection and no disruptive interactions between rods and cones were observed. Only at scotopic light levels did biological motion thresholds show a decline in performance. Detection of biological motion stimuli under rod vision is therefore not as efficient as under conditions favouring cones.

In conclusion, we found different effects of low light on perceptual sensitivity and cortical responses to coherent form and motion stimuli. These effects were not well explained by basic reductions in spatial vision, but indicate specific effects of low light on extra-striate visual processing. These results provide an initial insight into how patients with retinal disorders may perceive global form, motion and biological motion. For example, patients with cone disorders might be expected to show performance similar to our scotopic condition, in which controls relied on rods for vision. This would predict severely impaired global form

perception but relatively spared motion perception. However, there is also the possibility that retinal dystrophies present from a young age may lead to atypical development of mid-level vision. Future work will test this by carrying out these tasks with patient groups in the following two chapters (chapters 5&6).

Chapter 5. CORTICAL VISION IN CONE DISORDERS – BEHAVIOURAL DATA

5.1 INTRODUCTION

Hereditary disorders of cone function encompass a range of disorders resulting in loss of cone function. They can be stationary, affecting people from birth and showing little change in symptoms throughout life, or progressive, with typical onset in late childhood or early adulthood followed by a gradual loss of visual function (Michaelides, 2014). The main focus on this chapter is on patients with congenital achromatopsia (ACHM), a stationary cone disorder. The results for these patients along with a detailed discussion of their visual function are reported. A small number of individuals with progressive cone dystrophies (PCDs) are also considered. Results and discussion of these additional patients are given after discussion of the ACHM group. The PCD group was small and as such, care must be taken when drawing conclusions about their vision, however they allow some insight into changes in cortical visual function following the late-onset loss of cones.

Patients were tested on coherent form, motion, biological motion perception and contrast sensitivity tests. These tests were all as described in the control chapter (chapter 4). ACHM (stationary) and PCD (progressive) patients had their data compared to the control group described in chapter 4.

Previous research into visual function in disorders of cone function has focussed on early-level visual functions such as acuity and contrast sensitivity (Eksandh, Kohl, & Wissinger, 2002; Hess, Nordby, & Pointer, 1987; Hess & Nordby, 1986a, 1986b; Johnson et al., 2004; Michaelides et al., 2005; Michel Michaelides, 2014; Sloan & Feiock, 1972; Sloan, 1954). For example, visual acuity in ACHM patients with *CNGA3* and *CNGB3* mutations has been reported in the range of 20/100-20/600 (Nishiguchi, Sandberg, Gorji, Berson, & Dryja, 2005).

In progressive cone dystrophies (PCD) acuity deteriorates over several years but typically ends up at around 20/200 (Michaelides, Hardcastle, Hunt, & Moore, 2006). Hess, Sharpe, & Nordby (1990), carried out a detailed study of vision in one ACHM patient reporting on spatial and temporal properties of their vision. Spatial and temporal acuity as well as contrast sensitivity were found to be impaired in photopic conditions; however, scotopic vision was comparable between the patient and a control, suggesting typical rod mediated vision (Hess et al., 1987; Hess & Nordby, 1986a, 1986b). In contrast to Hess et al (1990) some studies have reported atypical dark adaptation curves in ACHM patients indicating reduced scotopic sensitivity (Aboshiha, Luong, et al., 2014; Frey, Gordesch, Heilig, & Thaler, 1975; Simunovic, Regan, & Mollon, 2001)

To examine the effects of cone disorders on global form and motion processing, it is necessary to consider whether low-level impairments of contrast sensitivity, and restrictions of rod function play a role in the reduction of sensitivity. We have attempted to simulate these effects with normal observers by (a) testing global form and motion sensitivity with a diffusing screen that acts as a low pass filter for spatial frequencies (chapter 3); (b) by testing under scotopic levels of illumination (chapter 4).

The possible impact of long-term cone loss on the perception of global form, motion and biological motion is unclear. If, as in previous studies (Hess & Nordby, 1986a, 1986b) patients show normal basic scotopic vision (i.e. contrast sensitivity functions), then their scotopic mid-level visual processing may reveal developmental effects due to their atypical visual input, particularly in the stationary (congenital) group. Interestingly, a classic account of ACHM on the Pacific atoll Pingelap (Sacks, 1996) suggests that the affected islanders are proficient at night fishing (“They seem to be able to see the fish in their dim course underwater … as well as, or perhaps better than, anyone else”). Like coherent motion or biological motion processing, this real-world task may depend in part on integration of motion

signals. The present study is the first to test coherent motion and biological motion perception with this population in a laboratory setting.

Previous work with children with binocular congenital cataracts has found long-term impairments in global form and motion perception several years after cataract removal (Ellemberg et al., 2002; Lewis et al., 2002; Taylor et al., 2009). This suggests that early visual experience is key to normal development of form and motion perception. Biological motion perception, however, has been shown to be preserved in those treated for congenital cataracts (Hadad, Maurer, & Lewis, 2012) and those with amblyopia (Neri et al., 2007; Thompson, Troje, Hansen, & Hess, 2008). This suggests a relative sparing of biological motion perception following impoverished visual input compared to global form and motion. In the case of stationary disorders of cone function such as ACHM, patients have some patterned visual input from birth, however this is atypical and optimal only in low light situations. Progressive cone dystrophies, by contrast, allow for a period of normal visual development during early childhood. Comparing mid-level visual function in both stationary and progressive cone disorder patients with controls, allows us to investigate possible effects of cone dysfunction on visual development.

In the past no treatment has been available for inherited disorders of cone function and care has relied on optimising patients' existing vision. However, advances in gene therapy and stem cell therapy are now opening up the possibility of new treatments. Recent gene replacement therapy in animal models of ACHM have shown promising results (Banin et al., 2015; Komáromy et al., 2010) and have led to the planning of human clinical trials, which highlights the need to better understand visual function in these conditions. Success of these therapies will depend in part on the whole visual system's ability to adapt to new visual experience.

The current study aimed to further understanding into visual function in patients with cone disorders. This focussed first, in detail on patients with ACHM before considering a small group of patients with PCD. The study focussed on mid-and higher-level vision which had not previously been researched in these patient populations. Psychophysical measures across a range of light levels were used to investigate perception of global form, motion and biological motion in patients with progressive and stationary disorders of cone function.

5.2 METHODS

5.2.1 Participants

Eleven patients (mean age 28.6, standard deviation 7.4 years) with a diagnosis of ACHM ("stationary" group) and 5 patients (mean age 49, standard deviation 7.8 years) with a diagnosis of PCD ("progressive" group) completed the study within the Faculty of Brain Sciences, Division of Psychology and Language Sciences, University College London. Information sheets were provided and informed consent was taken before testing commenced. Results were compared with baseline data collected from 20 normally sighted participants (mean age 25.2, standard deviation 4.6 years). Results from these control participants have been reported in chapter 4.

Patients were recruited through referrals from their clinician (JA, MM) at Moorfields Eye Hospital. All patients had a diagnosis of ACHM or PCD based on both clinical symptoms and genotyping. Details of genotype and visual acuity for each participant can be found in Table 5.1. Details of contrast sensitivity and of fixation stability, recorded using a Nidek MP-1 microperimeter (Nidek Technologies, Padova, Italy) are also given where these test results were available. Acuity and contrast sensitivity tests were carried out using standard protocols and lighting conditions (85 cd/m^2). Microperimetry was carried out on a research basis and results have been published elsewhere (see Aboshiha, Dubis, et al., 2014).

Participant	Age	Gender	Genotype	Visual Acuity (LogMAR)			Contrast Sensitivity (LogCS)			Fixation Stability (%)[2]	
				Right Eye	Left Eye	Both Eyes	Right Eye	Left Eye	Both Eyes	Right Eye	Left Eye
S1	28.5	M	*CNGB3*	1	1.2	1	1.05	1.15	1.35	30	27
S2	35.8	F	*CNGB3*	0.88	1.1	0.88	1.05	1.1	1.2	N/A	N/A
S3	34.0	F	*CNGA3*	0.9	0.84	0.82	1.5	1.5	1.65	91	79
S4	25.3	M	*CNGB3*	0.72	0.80	0.64	1.75	1.55	1.85	100	96
S5	19.6	F	*CNGA3*	0.78	0.78	0.78	N/A	N/A	N/A	N/A	N/A
S6	31.5	M	*CNGB3*	0.86	0.84	0.84	1.35	1.35	1.40	85	99
S7	26.8	M	*CNGB3*	0.84	0.92	0.82	1.5	1.2	1.4	99	99
S8	42.3	F	*CNGA3*	1.00	1.00	1.00	N/A	N/A	N/A	N/A	N/A
S9	50.0	M	*CNGB3*	0.92	1.00	0.86	1.35	1.15	1.35	100	92
S10	20.6	M	*CNGB3*	0.88	0.86	0.82	1.35	1.35	1.5	100	87
S11	21.2	F	*CNGA3*	0.8	0.8	0.76	0.75	0.65	0.9	100	100

Table 5.1. Demographic and clinical details for the 11 stationary patients with molecularly proven achromatopsia

Participant	Age	Gender	Genotype	Visual Acuity (LogMAR)		
				Right Eye	Left Eye	Both Eyes
P1	51.2	M	*GUCA1A*	0.9	0.9	0.9
P2	36.7	F	*KCNV2*	0.8	0.9	0.8
P3	47.3	F	*KCNV2*	1.20	1.78	1.20
P4	52.3	F	*KCNV2*	1.00	1.08	0.92
P5	57.5	M	*RIMS1*	1.08	1.00	1.00

Table 5.2. Demographic and clinical details for the 5 progressive patients.

[2] Fixation was recorded with a Nidek MP1 Microperimeter (Nidek Technologies, Padova, Italy). Participants were required to fixate a cross subtending 2°. The number given is the percentage of fixation within the central 4° surrounding the fixation target over a thirty second period.

5.2.2 Tests Completed

Patients completed tests of coherent form, coherent motion, biological motion processing, and contrast sensitivity. The four tests were completed by all patients with the exception of the contrast sensitivity test which 2 of the stationary patients did not complete.

Details of the stimulus design and task procedure can be found in the General Methods (chapter 2). All tasks were carried out as described there with additional features described below.

5.2.3 Light Levels

The light levels and procedure used in this experiment were the same as those described in the previous chapter (chapter 4).

To recap: Four light levels were used to assess the relative contribution of rods and cones to perceptual sensitivity and cortical EEG responses. Conditions were created using neutral density filters over the display monitor (Sabre International Ltd, UK) with no other light source in the room.

The light levels were photopic (8.7 cd/m^2), high mesopic (0.8 cd/m^2), low mesopic ($2.7x10^{-2}$ cd/m^2) and scotopic ($8.7x10^{-4}$ cd/m^2). The values here refer to the luminance of the dots/lines making up the stimuli; these were presented against a black background with a 3.24 Log Weber Contrast (LogWC) for each light level. Behavioural tests were completed under the four light conditions while EEG tests were completed under the high mesopic and scotopic conditions.

As with the controls (chapter 4) a subset of four patients (S1, S2, S11 and S12) had their pupil size measured whilst viewing the form stimulus in order in order to calculate retinal

illuminance in log scotopic trolands. This confirmed that the patients were experiencing light levels within the photopic, mesopic and scotopic ranges in each corresponding light condition. The only exception to this was patient S2 who was just inside the mesopic range when viewing the photopic stimulus due to her small pupil size. Appendix VI gives pupil size and log scotopic troland measurements for the four patients in each light condition.

The order of light levels was counterbalanced so that half of the participants completed the high mesopic and photopic conditions first while half completed the scotopic and low mesopic first. All participants were dark adapted before the tests. 30 minutes of dark adaptation took place before the scotopic / low mesopic tests and 10 minutes adaptation took place before the high mesopic / photopic conditions. Adaptation was achieved using blackout goggles (Mindfold Inc., USA).

Participants began by completing a practice session, which included all behavioural tests, completed in the photopic condition. This involved three runs of the form, motion and biological motion tests, with each run containing 30 trials. Participants also completed one run of the contrast sensitivity test which contained 100 trials. Thresholds across the form, motion and biological motion tests were compared to assess the consistency of each participant's performance. 14 of the 16 participants showed consistent threshold results after three runs of the tests. The remaining 2 participants completed an additional 2 runs of each test after which their results were stable.

For the main experiment, participants completed three runs each of the form, motion and biological tests in each light condition. Each run contained 30 trials. Participants also completed one run of the contrast sensitivity test in each light condition, containing 100 trials.

5.3 RESULTS – ACHM (STATIONARY) PATIENTS

5.3.1 Form, Motion and Biological Motion

The Shapiro-Wilk test of normality was used to check whether coherence thresholds departed from normal distributions in each test and participant group. These revealed that many results were not normally distributed (see Table 5.3) therefore all data was log transformed for further analysis (Table 5.3).

		Original		**Transformed**	
		Controls	Stationary	Controls	Stationary
Photopic	form	0.490	0.577	0.241	0.734
	motion	**0.009***	**0.006***	0.167	0.048
	bmotion	**<0.01***	**<0.01***	0.072	0.016
H.Mesopic	form	0.298	0.412	0.911	0.589
	motion	0.076	0.161	0.762	0.530
	bmotion	**<0.01***	**0.005***	0.601	0.268
L.Mesopic	form	**0.038***	**0.037***	0.067	0.211
	motion	**0.001***	**0.044***	0.072	0.282
	bmotion	**0.001***	**0.033***	0.658	0.777
Scotopic	form	**0.014***	0.123	0.270	0.281
	motion	**0.001***	**0.029***	0.249	0.208
	bmotion	**0.008***	0.105	0.115	0.805

Table 5.3. p-values from the Shapiro-Wilk test of normality. Values are given for group results of each test in each light condition, in original data and log-transformed data. P-values <0.05(highlighted red) indicate that the distribution departs significantly from the normal.

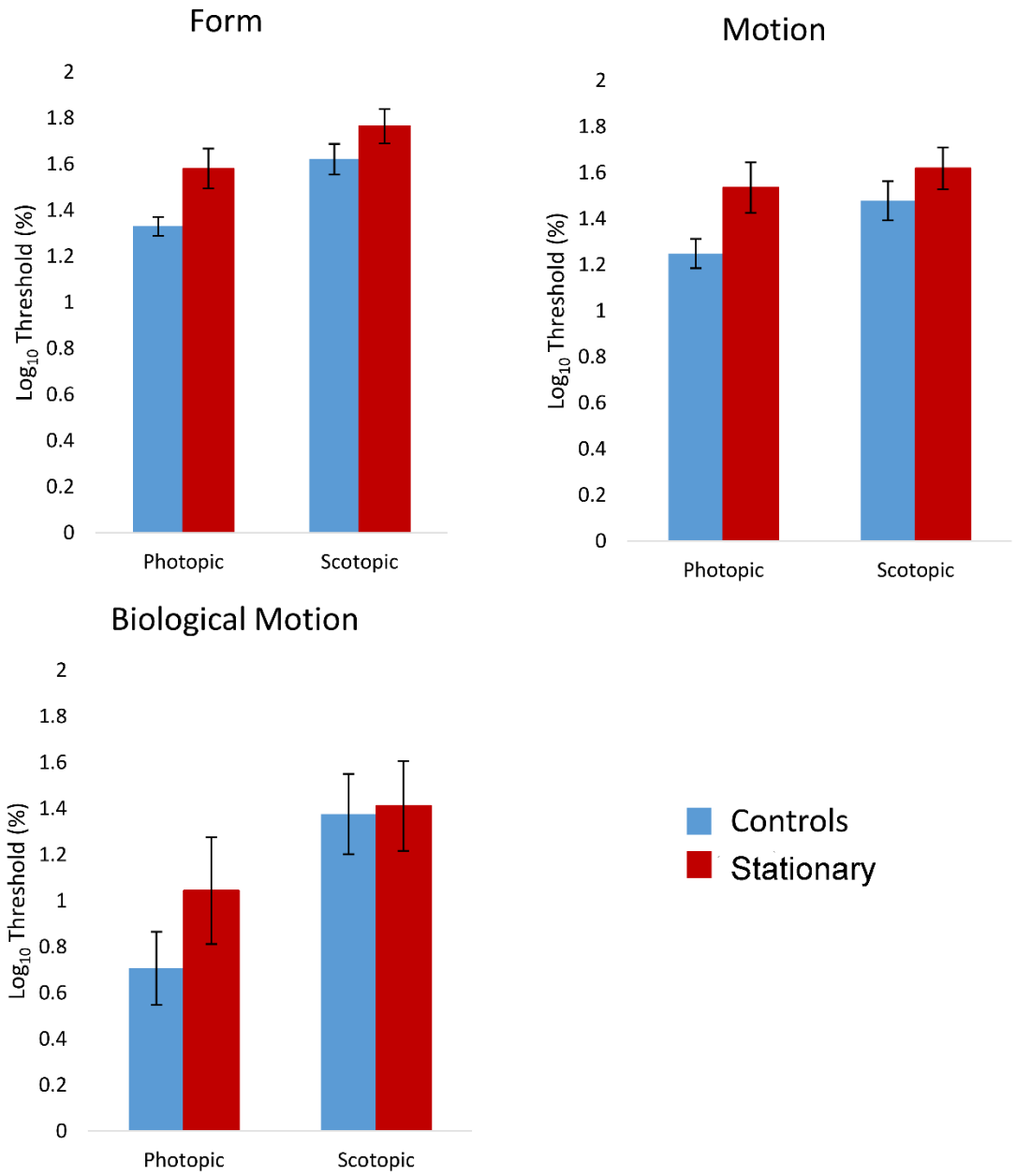

Figure 5.1. Patient and control log_{10} coherence thresholds for form, motion and biological motion tasks under two light levels. Error bars represent 95% confidence intervals.

Results in the first three light conditions (photopic, high mesopic and low mesopic) showed little variation, therefore comparisons are made between the photopic and scotopic conditions only. Full results from all four light levels are given in appendix VII.

Figure 5.1 shows the behavioural thresholds for patients and controls in photopic and scotopic conditions. The patients had their thresholds for each test compared to the control group using repeated measures ANOVAs.

Overall, patients were significantly worse than controls on the global form ($F(1,29) = 21.867$, $p<0.001$) and global motion ($F(1,29) = 12.878$, $p=0.001$) tests but not on the biological motion test ($F(1,29) = 2.317$, $p = 0.139$). There was a significant effect of light level on all three tests (form: $F(1,29) = 92.103$, $p<0.001$; motion: $F(1,29) = 29.512$, $p<0.001$; biological motion: $F(1,29) = 54.971$, $p<0.001$). There was also a significant group x light level interaction for all three tests (form: $F(1,29) = 4.666$, $p = 0.039$; motion: $F(1,29) = 6.417$, $p=0.017$; biological motion: $F(1,29) = 4.657$, $p = 0.039$). This suggests that light affected sensitivity in the two groups. This can be seen in Figure 5.1 with patients' thresholds showing less deterioration with luminance compared to controls.

A set of planned comparisons between patients and controls was carried out to compare thresholds in the scotopic condition. In this condition patients and controls are, in theory, matched in the sense that each group has to rely only on rod photoreceptors. Any differences between groups may reflect atypical rod function and/or atypical cortical visual processing in the patient group. A comparison of patients and controls in the scotopic condition showed significantly worse scotopic performance in patients on the form task ($t(29) = -2.650$, $p= 0.013$) but not for motion ($t(29) = -1.965$, $p = 0.059$) or biological motion ($t(29) = -0.246$, $p = 0.807$), although the motion result approaches significance; see Figure 5.1, "Scotopic" columns.

To directly compare results across the three tests, z-scores were calculated from log thresholds. These scores, plotted in Figure 5.2, normalise data for each test to the control group such that a z-score of 0 represents a threshold matching the controls. Z-scores greater than 0 represent thresholds higher (worse) than controls, and those below 0 represent thresholds lower (better) than controls. This normalisation was necessary to make

direct comparisons across tests, which are not necessarily comparable in terms of difficulty. The 95% confidence intervals for z-scores in Figure 5.2 also show conditions in which patients differ significantly from controls (i.e. mean z-scores are significantly different from 0), as tested earlier in the planned comparison of patients and controls in scotopic conditions.

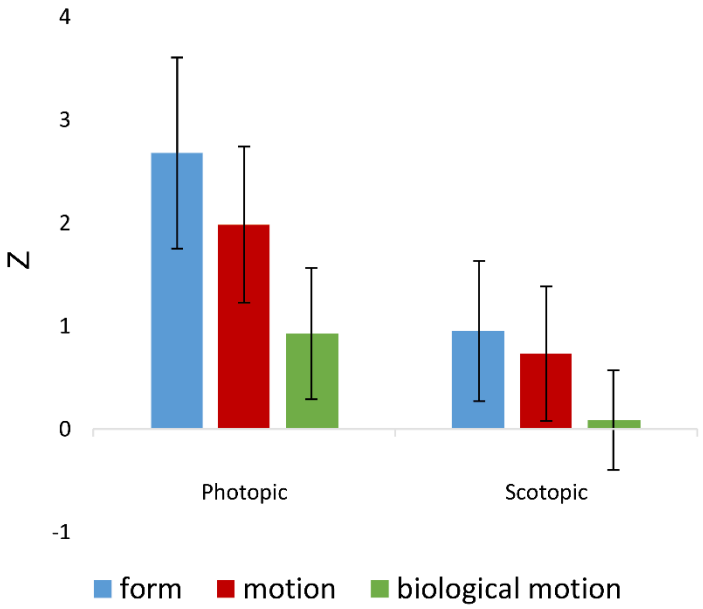

Figure 5.2. Mean z-scores based on form, motion and biological motion thresholds in the patient group compared to the baseline of control data. Error bars represent 95% confidence intervals.

A repeated measures ANOVA of z-scores (Figure 5.2) found a main effect of test type ($F(2,20) = 35.216$, $p<0.001$), indicating that the pattern of performance across the three tests was different to that of the controls. Pairwise comparisons with a Bonferroni correction revealed that this effect was driven by differences between the biological motion result (mean z = 0.507) and the other two tests (form mean z = 1.815; motion mean z = 1.358); with biological motion perception being relatively spared compared to form and motion perception; (see Figure 5.2). There was also a main effect of light on the patients' z scores

(F(1,10) = 25.283, p=0.001), indicating that overall, patients were affected differently to controls by changes in light level. Figure 5.2 shows that patients' performance became more similar to controls (i.e., z scores approached 0) as the light level reduced. Nonetheless, their performance on global form and motion remained worse than controls in the scotopic condition, where both groups presumably depended entirely on information transmitted by rods. There was also a significant interaction between test and light levels (F(2,20) = 3.604, p = 0.046) indicating that differences in patient vs control performance across tests were differentially affected by reductions in luminance. As Figure 5.2 shows, for form and motion, differences between patients and controls were marked (z scores were high), but reduced with light level. In contrast, for biological motion, differences were lower (z scores were nearer 0), and these changed less across light levels.

5.3.2 Contrast Sensitivity Functions

Figure 5.3 shows measured photopic and scotopic CSF curves for each patient (CSF data from all four light levels is shown in appendix VII). Two of the patients were unable to attend follow-up appointments to have their CSFs measured, so results are given for 9/11 of the patients. Shaded regions represent the 95% confidence intervals of control data for each light condition. Patient CSFs falling within the 95% CI are therefore comparable to controls. This was only expected under scotopic light levels. Three patients (S6, S7, S9; Figure 5.3, "†") had scotopic CSFs (red curves in Figure 5.3) comparable to controls. Two of the nine patients had severe difficulties with the task, with no recordable responses in photopic or scotopic conditions (S5 and S9; Figure 5.3, "‡"). For these patients the CSF task was particularly difficult relative to the mid-level tests. We first analyse summary statistics describing CSF changes across the two light levels in patient and control groups. This is followed by analyses related to individual differences in CSFs. In particular, we examine scotopic form, motion and biological motion thresholds in the subset of patients whose scotopic CSFs were within the normal range.

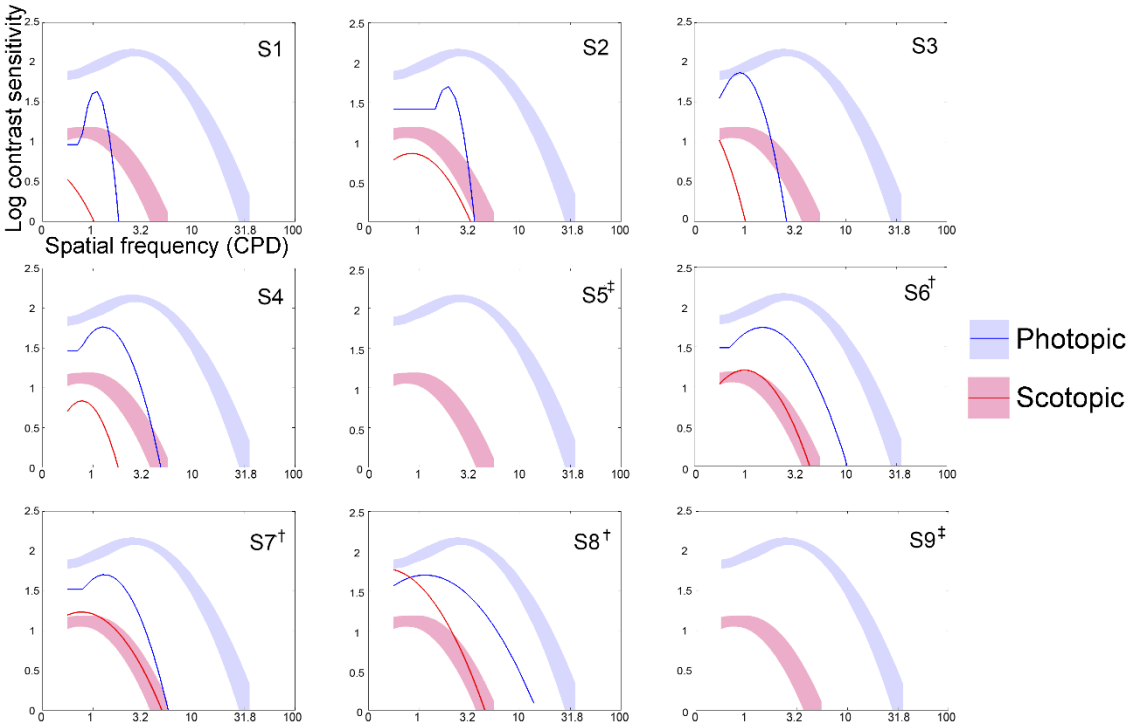

Figure 5.3. Contrast sensitivity functions for individual patients. Solid lines represent CSFs for each light condition. Shaded areas represent the 95% confidence intervals of control data. Patients with CSFs within the normal scotopic range are marked †. Those who could not complete all conditions are marked ‡.

5.3.3 Form, Motion and Biological Motion Perception in Patients with Normal Scotopic CSFs

As Figure 5.3 shows, all patients had impaired spatial vision in photopic conditions (blue curves). However, three of the nine patients whose CSFs were measured had scotopic CSFs (red curves) at least within the control range (S6, S7 and S8; S8 had scotopic sensitivity better than the 95% control range at low spatial frequencies). These results show that there was considerable variability in spatial vision in the patient groups. Patients with scotopic CSFs comparable to those of controls (S6, S7 and S8) had their scotopic form, motion and biological results further examined.

Figure 5.4 shows control group data in the scotopic condition, plotted alongside the individual data from patients with scotopic CSFs comparable to controls. The three patients had elevated scotopic form thresholds compared to controls. However, their motion and biological motion thresholds were better than the group average (see Figure 5.1). Their motion thresholds were within or just outside the control 95% CI, and their biological motion perception was notably good, with two of the three patients (S6 and S8) showing biological motion thresholds better than the control 95% CI (Figure 5.4).

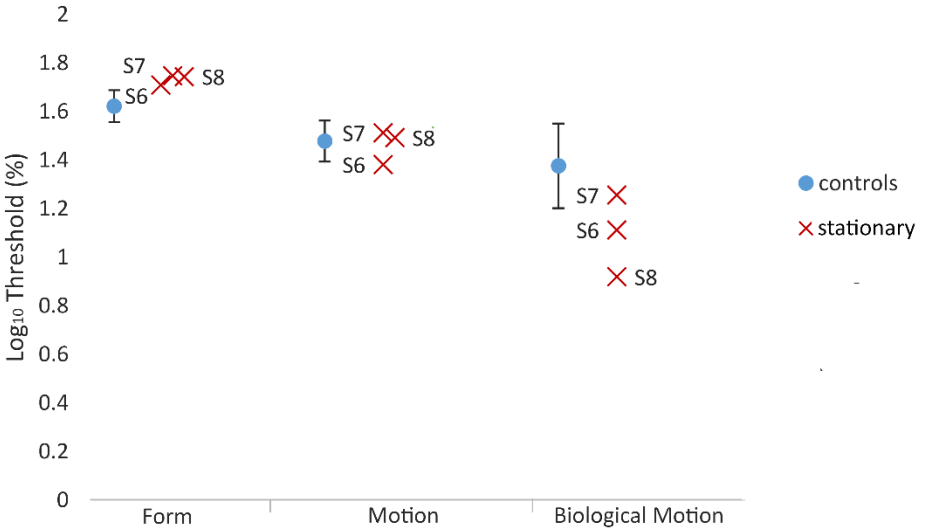

Figure 5.4. Form, motion and biological motion thresholds in the scotopic condition. Control data represents the group mean, error bars represent the 95% confidence interval. Individual patients (S6, S7 and S8) who had scotopic CSFs comparable to controls are plotted individually (Xs).

Departures from the control 95% CI in Figure 5.4 are informative, but to test stringently for significant differences against controls in this subset of patients, we adjusted for the four multiple comparisons (i.e. three individuals considered in Figure 5.4) in each test. We asked whether each patient's log threshold differed from the control group mean using a two-tailed one-sample t-test, with a significance threshold calculated using the Šidák correction to give

a familywise type I error rate of 0.05 (the corrected p value is 0.0170). The results of these comparisons are given in Table 5.4. As Table 5.4 shows, two of three patients demonstrated superior biological motion perception to controls (the remaining patient was comparable to controls), and three of three demonstrated coherent motion perception comparable to controls.

	N sig. different to controls		
	better	worse	not different
Form	-	2	1
Motion	-	-	3
Bio Motion	2	-	1

Table 5.4. Summary of results of one sample t-tests corrected for multiple comparisons, comparing patients with CSFs in the normal range with controls on each test.

Neither individual differences in CSFs (Figure 5.3), nor patterns of performance on the main tasks in those patients with normal scotopic CSFs (Table 5.4), are well accounted for by differences in age or genotype (see Table 5.1). These three participants had ages (31.5, 26.8 and 42.3 years) within the middle of the overall range for the patient group (19.6-50.0 years) and had both *CNGB3* (N=2) and *CNGA3* (N=1) mutations. Patients with superior biological motion perception (S6 and S8) were the older two of these patients, one with each of *CNGA3* and *CNGB3*. In those with minimal CSF responses (S5, S9) there is also no consistency in age or genotype suggesting these were not responsible for their results.

In summary, the sub-group of 3 patients who had normal scotopic spatial vision showed coherent motion and biological motion perception comparable to or better than controls. Notably, biological motion perception in 2 of 3 patients was superior to controls. This potentially reveals a developmental specialisation in some patients born without cone

function, who have retained good rod-based spatial vision comparable or better than controls, for rod-based biological motion perception (2 of 3 patients).

5.4 DISCUSSION – ACHM (STATIONARY) PATIENTS

The current results aimed to understand the impact of ACHM on mid-level visual perception. We were particularly interested in whether an absence of cones leads to differences in cortical visual processing which are not explained simply by changes in low-level visual perception. Such differences compared with controls could be due to visual development with atypical input.

Results showed that patients had differential impairments in mid-level vision across different tests. ANOVAs of log thresholds found most evidence for impairments of global form and motion, rather than biological motion. Direct comparisons of z-scores across tests revealed differential impairments across the three tests, with biological motion the least impaired. Tests in scotopic conditions in which patients and controls are both dependent on their rods for vision revealed impairments in form perception, but only marginal impairments for motion and none for biological motion perception.

These results suggest that a congenital absence of cones allows for normal or near-normal development of some kinds of (scotopic) mid-level visual processing, including motion and biological motion perception, but not form perception. It may be that an absence of cones from birth allows for some specialisation for scotopic vision, particularly for motion perception.

Deficits relative to controls in scotopic conditions may be due to two main factors. First, they could be the outcome of atypical visual development. Second, results could be due to a loss of rod function relative to controls. This has been suggested in ACHM (Aboshiha, Luong, et al., 2014; Frey et al., 1975; Khan et al., 2007; Nishiguchi et al., 2005; Simunovic et al., 2001; Sundin et al., 2000). We gained insight into the extent to which there may have been such disruption from our measures of CSFs across the four light levels.

CSF results showed that, on average, patients had low-level deficits in spatial vision across photopic and scotopic light conditions. These effects did not seem to be explained by either the age of participants or their genotype, which varied across both the subgroup of participants with normal scotopic CSF and those who showed minimal CSF responses.

In participants with atypical scotopic CSF results, it is possible that there is rod dysfunction alongside cone dysfunction. Previous detailed reports of rod function in a single patient with ACHM described rod mediated vision that was comparable to controls (Hess et al., 1987; Hess & Nordby, 1986a, 1986b). However, there is variation across individuals. Some cases of ACHM with associated rod dysfunction have been reported (Khan et al., 2007; Nishiguchi et al., 2005; Sundin et al., 2000) and atypical dark adaptation curves have been found (Aboshiha, Luong, et al., 2014; Frey et al., 1975; Simunovic et al., 2001). Khan et al. (2007) reported on three sisters with cone dystrophy caused by the *CNGB3* genotype. Rod ERG revealed reduced b-wave amplitudes indicating loss of rod function. The results of our CSF test support the view that a majority of patients had associated rod dysfunction with 6/9 patients demonstrating reduced spatial vision at scotopic light levels.

Possible reasons for rod dysfunction in ACHM patients may be the result of a bystander effect in which the loss of one class of photoreceptor contributes the decline of other photoreceptors through the transfer of material through rod-cone gap junctions (Besharse & Bok, 2011).

Most strikingly, two of the three patients with normal scotopic CSFs showed superior scotopic biological motion perception compared to the sample of controls with healthy vision. This implies that when low-level spatial vision is not impaired, some aspects of scotopic extrastriate vision in patients with ACHM can be better than in healthy controls. This would be explained by a developmental specialisation for visual processing using only the rod signal. Whether this advantage for biological motion processing has any relationship to the

observation by Sacks (Sacks, 1996) that Pingelap islanders with ACHM are as good or better than unaffected observers at seeing fish moving in the water at night is an interesting question for further research.

The overall sparing of global motion and biological motion perception relative to form is in line with evidence that the rod system may be optimised for motion perception relative to form. Rods feed into magnocellular mechanisms within the visual cortex (Chen & Sampath, 2013; B. B. Lee et al., 1997; Sun et al., 2001), which in turn support dorsal stream processing and motion perception (Maunsell, Nealey, & DePriest, 1990). Parvocellular pathways which support the perception of form via the ventral stream (Wilkinson et al., 2000; Wilson, Wilkinson, & Asaad, 1997; Wilson & Wilkinson, 1998), receive the majority of their input from cones (Lee et al., 1997) and it is therefore understandable that cone disorder patients would demonstrate impairments in form perception. Scotopic form impairments were seen in 2/ 3 patients with normal scotopic CSF despite otherwise normal low-level vision. The cone signal therefore appears to play a crucial role in the development of perception of global form, as global form is impaired relative to controls even in scotopic conditions in which both groups have to rely on rods, and even in those patients who show no scotopic spatial vision loss. In contrast, the rod signal appears to be sufficient for development of a relatively good level of extrastriate motion (particularly biological motion) processing.

The sparing of biological motion perception in ACHM patients follows similar findings in patients with congenital cataracts and amblyopia (Hadad et al., 2012; Neri et al., 2007; Thompson et al., 2008). These results all point towards biological motion perception being spared when vision is impaired. ACHM, cataract and amblyopia patients reported in these studies have in common substantial visual impairment during early development. Visual development in these patients may therefore have specialised to optimise detection of biological motion when visual information is sparse.

In conclusion, stationary ACHM patients showed impairments in coherent form and motion but not biological motion, suggesting rod mediated vision is sufficient for the development of biological motion perception. Of patients with normal scotopic low-level sensitivity 2/3 demonstrated superior biological motion sensitivity to controls. Cone dysfunction syndromes are a candidate for stem cell and gene therapy (Banin et al., 2015; Komáromy et al., 2010; Sundaram et al., 2014; Yang et al., 2014; Ye et al., 2014). The success of any new therapies will be dependent on the plasticity of both the retina and the visual brain to adapt to new visual input. The extent to which their mid- and higher-level visual processing can further be reorganised – for example, to improve the perception of coherent form given a newly available cone signal – is an important open question.

5.5 RESULTS – PCD (PROGRESSIVE) PATIENTS

In addition to the ACHM patient group, 5 patients with progressive cone dystrophies completed tests of form, motion, biological motion and contrast sensitivity.

This patient group was too small and heterogeneous to perform rigorous statistical analysis on, however their results are nonetheless of interest and provide insight into how mid-level vision functions in patients who have lost their cones in late childhood/ early adulthood.

As with the controls and stationary groups, coherence thresholds were log transformed for plotting alongside the control and ACHM data. Patients are plotted individually. Little variation was seen between the mesopic / photopic light levels so, as with the stationary patients, results are given for the photopic and scotopic conditions. Results for each test in all four light conditions are given in a table in appendix VII.

5.5.1 Form, Motion and Biological Motion

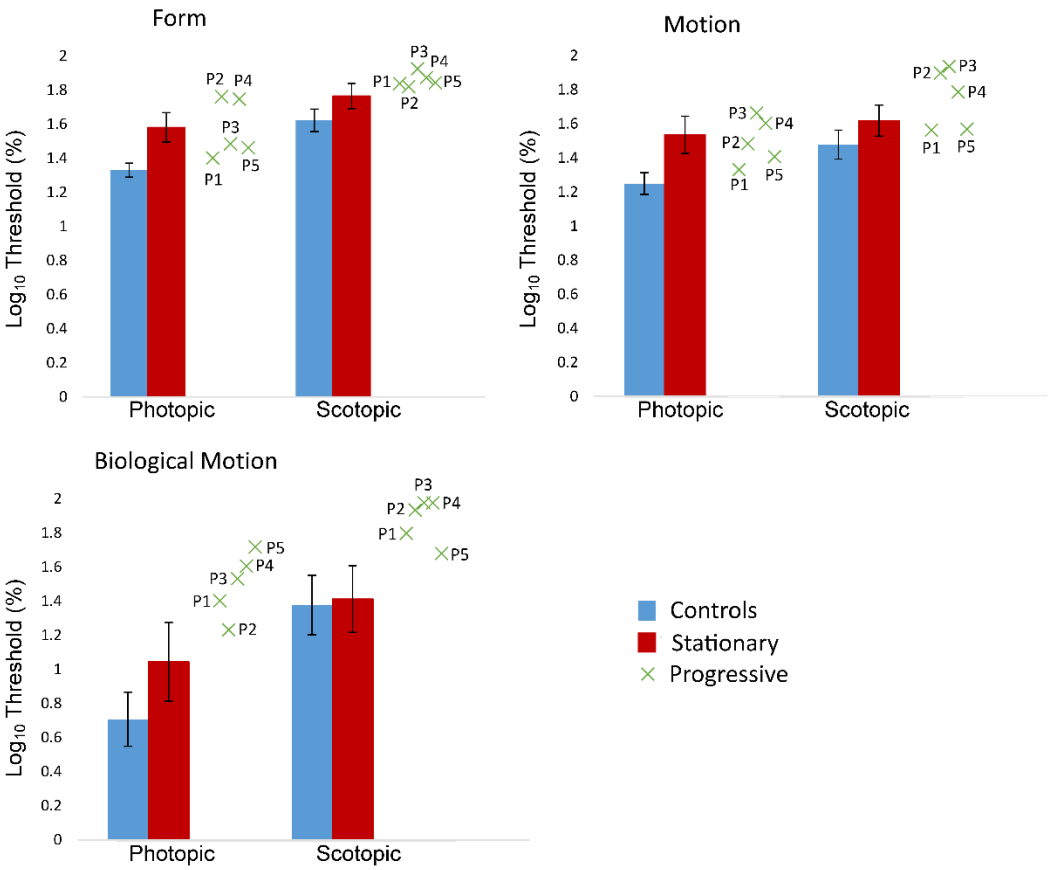

Figure 5.5. Patient and control log_{10} thresholds for form, motion and biological motion tasks under two light levels. Error bars represent 95% confidence intervals.

Figure 5.5 shows log thresholds for form, motion and biological motion tests across the two light levels for the two patient groups and controls. Progressive patients are shown individually because of their small group size. Like stationary patients, progressive patients show impairments relative to the control group.

Across the two patient groups, form and motion results appear similar, with a tendency for greater impairment in the PCD group in the scotopic condition. However, biological motion perception was markedly worse in the PCD group compared to the stationary group, especially in the scotopic condition.

Results were converted to z-scores to allow for a visual comparison across the three tests with each patient plotted individually (Figure 5.6). These show that the PCD patients were impaired across the tests and light conditions relative to controls (all scores > 0). The three tests show a similar level of impairment to one another in each light condition. 2/5 of the PCD patients (P2 and P4) were particularly impaired on the photopic form test as demonstrated here and in Figure 5.5.

These results differed from the stationary group (Figure 5.2). Stationary patients showed less impairment relative to controls in scotopic conditions than photopic whereas progressive patients appear comparably impaired across both light levels. Stationary patients also showed scotopic biological motion thresholds comparable to controls but this is not the case for progressive patients.

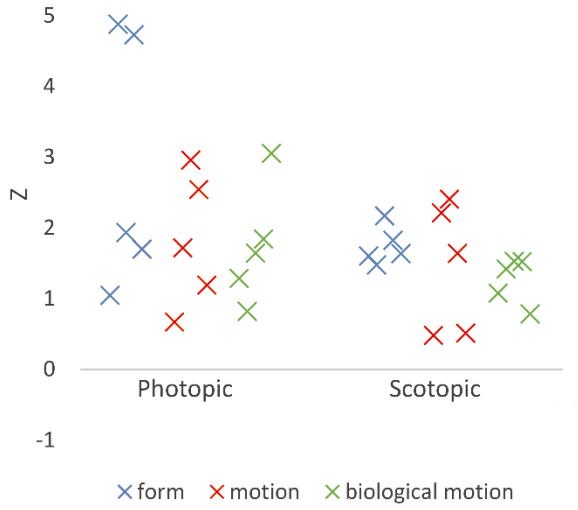

Figure 5.6. Mean z-scores based on form, motion and biological motion thresholds in the patient group compared to the baseline of control data.

5.5.2 Contrast Sensitivity Functions

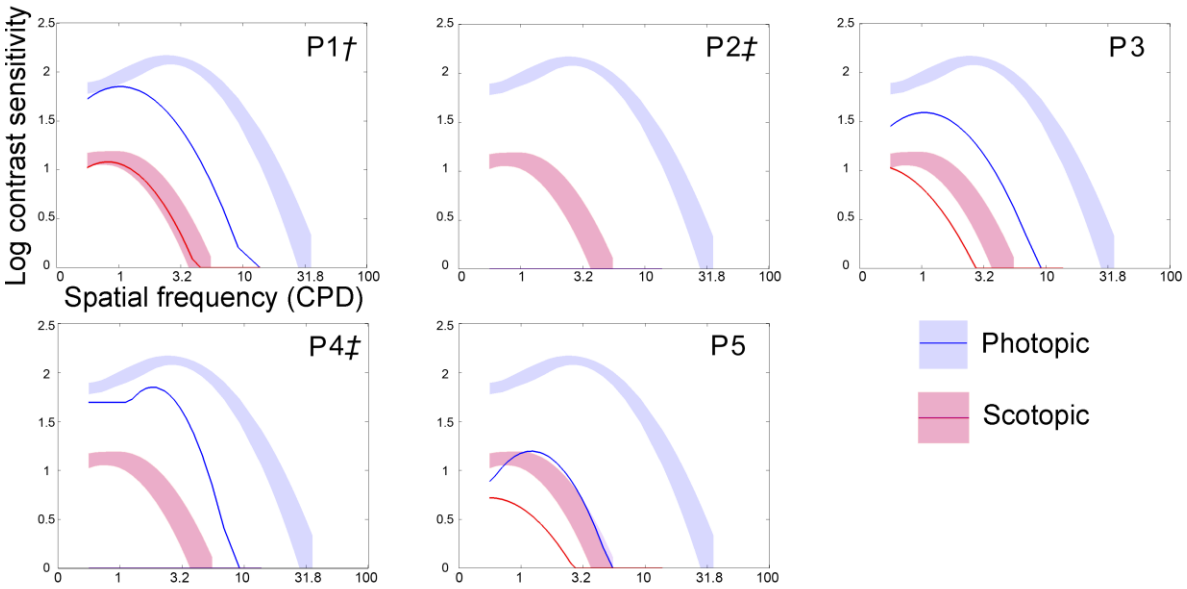

Figure 5.7. Contrast sensitivity functions for 5 PCD patients. Solid lines represent CSFs for each light condition. Shaded areas represent the 95% confidence intervals of control data. Patients with CSFs within the normal scotopic range are marked †. Those who could not complete all conditions are marked ‡.

Figure 5.7 shows CSFs for each progressive patient in the photopic (blur curve) and scotopic (red curve) conditions. CSFs for the 5 progressive patients show some variation. One patient (P2) was unable to complete the test in any of the light conditions. Of the remaining four patients, one demonstrated normal scotopic sensitivity (P1). All other conditions were below the control level in photopic and scotopic conditions.

These results highlight the variation seen in these patients. Some of these results may be linked to genotype but it is difficult to confirm this with this small group. P1, for example showed the best performance on the CSF test and also had some of the best acuity (second only to P2 in this group, see Table 5.2). P1 also had a different genotype (*GUCA1A)* to the

other patients and so it is possible this allows for better retention of good spatial vision. However, more patients with the *GUCA1A* genotype would need to be seen to confirm this.

P1 had his results examined further to determine whether his normal scotopic CSF results translated into normal results on the form, motion and biological motion tests. However, this was not found to be the case and performance appeared impaired relative to controls on tests of form and biological motion (see Figure 5.8). This patient's motion threshold was just within the control 95% confidence interval.

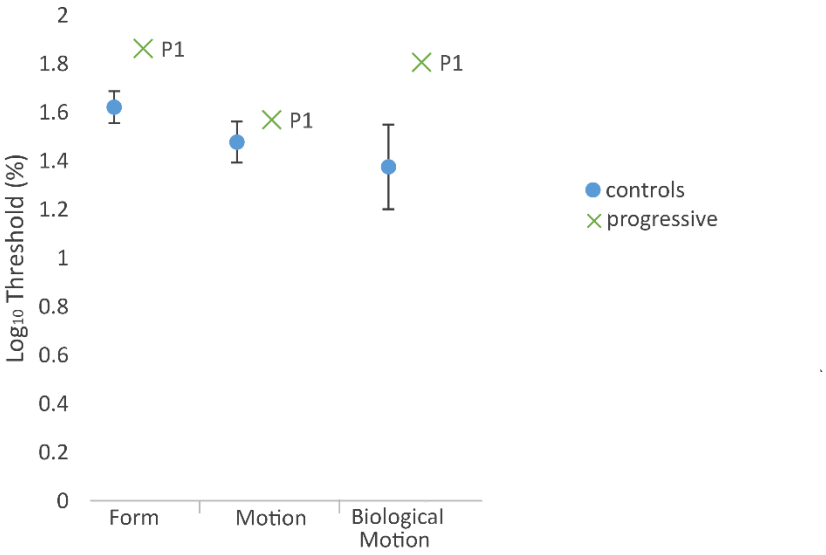

Figure 5.8. Form, motion and biological motion thresholds in the scotopic condition. Control data represents the group mean, error bars represent the 95% confidence interval. One individual patient (P1) who had scotopic CSF comparable to controls is plotted individually (X).

5.6 DISCUSSION – PCD (PROGRESSIVE) PATIENTS

Patients with progressive cone dystrophies have experienced normal vision up until the onset of sight loss in their late childhood / early adulthood. Deficits seen in these patients have therefore come about after normal childhood visual development of extrastriate visual processing.

The results from the PCD group show that individually all have worse form, and biological motion perception than controls and all but one have worse motion perception. These effects were true across all photopic and scotopic tests. In one patient with normal scotopic contrast sensitivity, performance on the form and biological motion tests was still worse than controls and only the motion threshold reached a normal level.

Interestingly, unlike the stationary patients, no advantage to biological motion perception was observed in the progressive group. This also differs from previous findings of patients with cataracts and amblyopia who had spared biological motion perception relative to other types of mid-level vision (Hadad et al., 2012; Neri et al., 2007). This suggests that preservation of biological motion perception may come about during adaptation in early visual development.

The finding that the 4/5 progressive patients showed a loss of scotopic sensitivity on the CSF test suggests there is a loss of rod sensitivity in this group. Patients were selected on the basis of having minimal rod disruption, however, the loss of rod function is common in cone dystrophies and not always predictable (Michaelides et al., 2006). These patients may therefore have been demonstrating early changes in rod sensitivity which could have contributed to their mid-level scotopic impairments. However, the fact that mid-level impairments remained in coherent form and biological motion perception in the one

progressive patient with normal scotopic sensitivity suggests that PCD may contribute to a loss of mid-level vision, independent of low-level impairments.

In conclusion, PCD led to a loss of sensitivity of form, motion and biological motion perception. This occurred across light conditions and may indicate a loss of rod function alongside cone dysfunction. While the small group size make comparison to the stationary group difficult, results hint at differences between the visual function in these two groups with PCD representing a more global loss of extrastriate visual function and ACHM representing a more uneven pattern of loss that suggests some specialisation in response to atypical input during development.

Chapter 6. CORTICAL VISION IN CONE DISORDERS – SSVEP DATA

6.1 INTRODUCTION

The previous chapter reported behavioural measures of coherent form, motion and biological motion processing in patients with stationary and progressive cone disorders. Stationary patients demonstrated impairments in coherent form and motion perception but spared biological motion perception. Progressive patients showed impairments on all three tests relative to controls

To further examine how visual perception is affected in these patients, SSVEP tests of coherent form and motion perception were carried out. No previous EEG measures of mid-level cortical visual processing have been published on patients with cone disorders and whether their visual deficits reflect atypical organisation of neural processing remains elusive. fMRI work carried out with ACHM patients has shown evidence of atypical activation suggestive of reorganisation within the primary visual cortex (Baseler et al., 2002). The authors identified rod-based activation within the patients' foveal projection zone, usually only activated by cone input from the fovea. This suggested that these patients had undergone cortical reorganisation allowing rod input to generate a neural response in a region typically free from rod projections.

Looking at both topographical data and amplitude measures across the scalp the current study aimed to see whether EEG signals resulting from global form and motion stimulation were atypical in cone disorder patients. Patients were compared to the control EEG data collected in chapter 4. The patients underwent the same test procedure as the controls, described in chapter 4. Participants with PCD also completed EEG tests, however the small

group size meant that analysis of their data was uninformative. This was due to a combination of individual variation between the participants and a high degree of noise in the data. Topographic plots for the progressive group are shown in appendix VIII.

6.2 METHODS

6.2.1 Participants

Patients and controls are as described in chapters 4 (controls) and 5 (patients). S1-S9 of the stationary patients completed the VEP tests. S10 and S11 were unable to attend for the SSVEP session. All PCD patients (N=5) completed the EEG tests.

6.2.2 Tests completed

Patients completed SSVEP tests of coherent form and coherent motion perception. Biological motion SSVEPs were piloted but did not produce measurable responses (see appendix III for details).

Details of the stimulus design, task procedure and SSVEP data handling can all be found in the General Methods (chapter 2). All tasks were carried out as described there with additional features described below.

6.2.3 Light levels

As with the control dataset (chapter 4), SSVEP was carried out at high mesopic (0.8 cd/m^2) and scotopic (8.7x10^{-4} cd/m^2) light levels. Participants were dark adapted for 30 minutes before the SSVEP tests, using blackout goggles (Mindfold Inc., USA). The scotopic condition was always carried out first to allow for maximum dark adaptation in that condition.

6.2.4 Analysis

Patient and control data presented in this chapter are in the form of raw amplitudes. This is in contrast to the control data described in chapter 4 which used the T^2_{circ} analysis and

presented T^2_{circ} values in the topographic plots. The reason for using raw amplitude data here as opposed to T^2_{circ} is that the T^2_{circ} test is uninformative when dealing with small group sizes. No significant T^2_{circ} values were obtained for the patient group (N=9) using this analysis. However, the topography of the control data presented in chapter 4 is in agreement with the topography of the amplitude data presented here.

6.3 RESULTS

6.3.1 VEP Topography

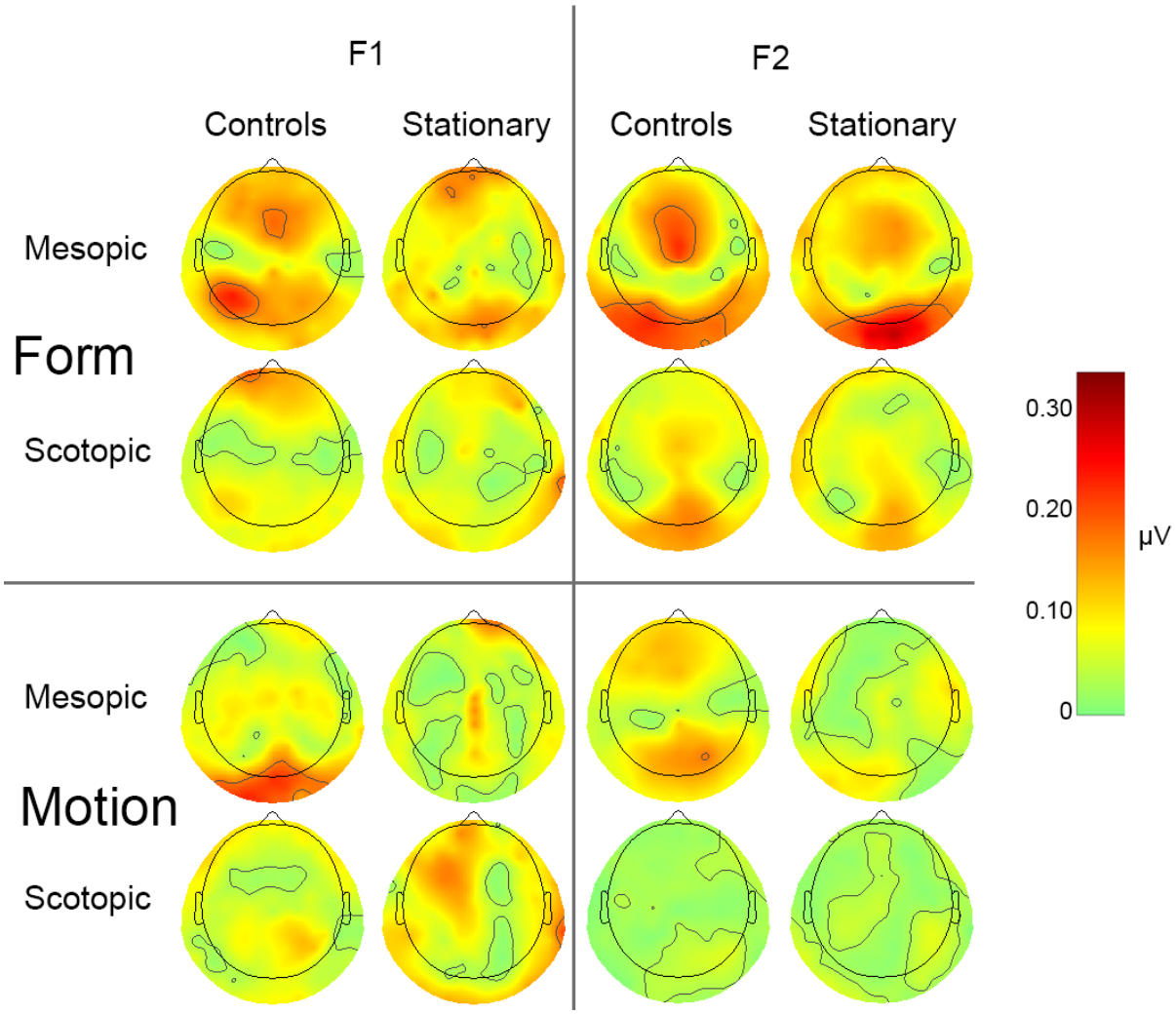

Figure 6.1. Topographic plots of average form and motion amplitudes (µV) for controls and stationary (ACHM) patients. Plots are shown for mesopic and scotopic conditions. F1 (global) and F2 (local) amplitudes have been plotted separately.

Topographic plots of control and stationary (ACHM) group data were generated and are shown in Figure 6.1.These show the VEP amplitude (µV) for each electrode, averaged across participants in each group. Responses are shown at the first harmonic (F1) sensitive

to changes in coherence of the form or motion stimulus and the second harmonic (F2) sensitive to local changes in the stimulus display. The very small group size of the PCD patients (N=5) meant that their EEG data were too noisy to analyse, even as mean amplitude. For reference, these noisy group topographic plots for PCD patients are presented in appendix VIII.

6.3.1.1 Mesopic Form and Motion F1

In mesopic conditions controls showed a form response peaking over the left occipital region and a motion response peaking over the central occipital pole as reported in chapter 4 and previous studies (Wattam-Bell et al, 2010). For the stationary group, form responses peaked in the occipital pole while motion responses showed an unclear pattern of activation. This suggests a more typical organisation of form than motion for patients in mesopic light.

6.3.1.2 Scotopic Form and Motion F1

Patients and controls showed a reduction in VEP amplitude in the scotopic condition compared to mesopic. In the control group, the pattern of activation for form responses remained consistent with the mesopic condition, peaking in the left occipital lobe. The motion response shifted from a central to a more lateral position. The stationary group showed a weak left occipital response to form similar to the patients, however there was an unclear pattern for motion responses.

6.3.1.3 Mesopic Form and Motion F2

Controls showed a mesopic F2 response overlying the occipital midline for form and motion stimuli, although this was reduced in the motion condition. The stationary group also showed this pattern for form and motion stimuli but again F2 motion responses were reduced relative to form.

6.3.1.4 Scotopic Form and Motion F2

Overall, as with F1 responses, scotopic F2 amplitudes were reduced. The controls and stationary group showed an occipital response in the form condition, mirroring their mesopic form F2 responses. As with the mesopic condition, motion F2 responses were reduced relative to form. Scotopic motion responses were minimal for both groups.

6.3.2 F1 Topographic Correlations

To determine in which circumstances scalp topographies were similar and dissimilar, F1 amplitudes across the whole scalp were correlated between participant groups (stationary, control), tests (form, motion) and light conditions (mesopic, scotopic). Results are shown in Table 6.1. For ease of visualisation, Figure 6.2 plots some key comparisons from this table.

			Control				Stationary			
			Form		Motion		Form		Motion	
			M	S	M	S	M	S	M	S
Control	Form	M	1	.547**	-0.036	0.036	.289**	0.138	-0.034	-.203*
		S	.547**	1	-0.079	.202*	.545**	.479**	.204*	0.003
	Motion	M	-0.036	-0.079	1	-0.057	.246**	0.136	0.033	-0.056
		S	0.036	.202*	-0.057	1	0.098	-0.111	0.179	-.295**
Stationary	Form	M	.289**	.545**	.246**	0.098	1	.362**	.284**	.189*
		S	0.138	.479**	0.136	-0.111	.362**	1	.280**	.356**
	Motion	M	-0.034	.204*	0.033	0.179	.284**	.280**	1	-0.011
		S	-.203*	0.003	-0.056	-.295**	.189*	.356**	-0.011	1

R=significant, p<0.01**
R=significant, p<0.05*
0.199>R>0.1
0.099>R>0
-0.011>R>-0.1
-0.11>R>-0.2
R=significant, p<0.01**

Table 6.1. Correlation between electrode amplitudes in form, motion, mesopic (M) and scotopic (S) conditions and across participant groups. Values represent Pearson's R. Those shown in the darkest red and blue represent significant positive and negative correlations.

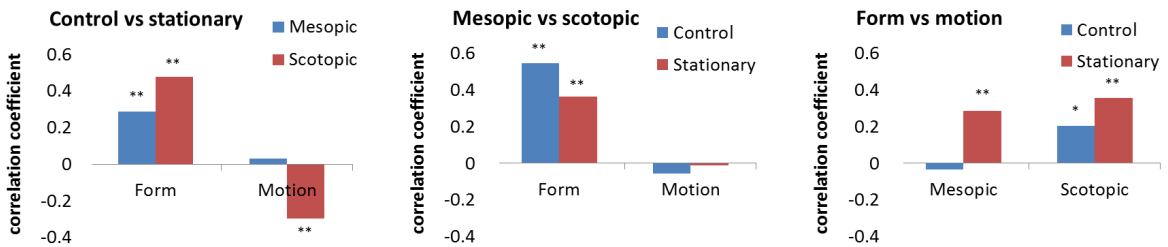

*Figure 6.2. Correlation coefficients of amplitudes across electrodes for controls vs. stationary patients (left), mesopic vs scotopic light levels (middle) and form vs motion stimuli (right). ** p<0.1, * p<0.05.*

In comparisons of control vs stationary group topographies (Figure 6.2, left), mesopic and scotopic form responses were significantly correlated across the two groups of participants. By contrast, motion responses were not correlated in the mesopic condition, and were significantly negatively correlated in the scotopic condition (see also Figure 6.2). This indicates that at both mesopic and scotopic levels, typical topographies for form coherence were preserved in the stationary group.

The lack of correlation between the stationary and control mesopic motion responses could indicate different patterns of activation or could be due to a weak response in one or both groups. Figure 6.3 (top left) shows individual electrode amplitudes of stationary vs controls. This shows that while the stationary group had weaker responses overall, both stationary and control groups had regions of high activation. This indicates that the lack of correlation between the two groups (for mesopic motion) does not only reflect a weak response in the patient group. In addition, the significant negative correlation (for scotopic motion) shows evidence for different topographies in that condition.

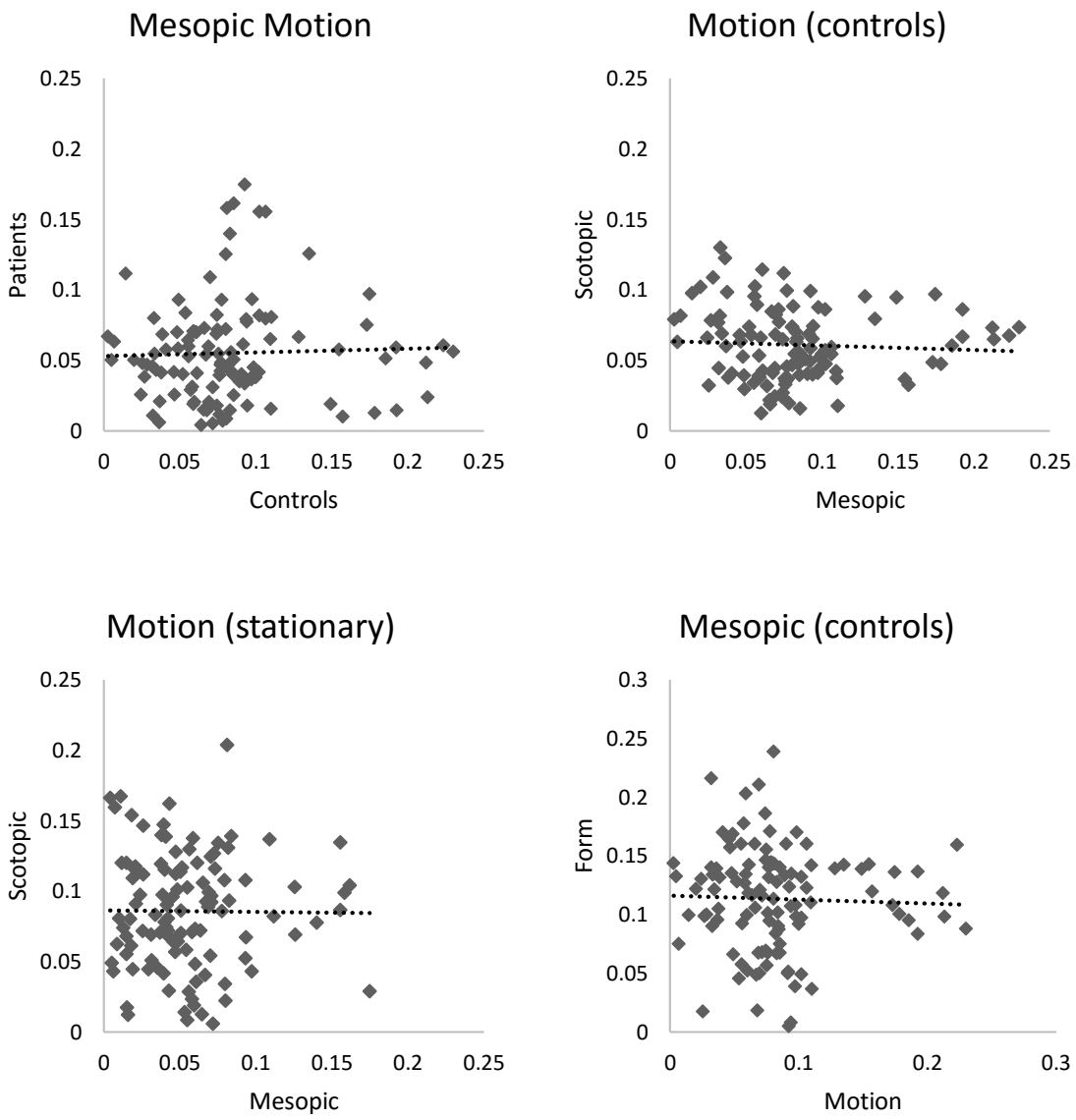

Figure 6.3. Non-significant correlations. Top left: controls vs. stationary mesopic motion responses; top right: scotopic vs mesopic motion responses (controls); bottom left: scotopic vs mesopic motion responses (stationary group); bottom right: form vs. motion mesopic responses (control group).

In comparisons of mesopic vs scotopic topographies for matching stimuli (Figure 6.2, middle), responses to the form stimulus were significantly correlated across light levels in both the control and stationary groups. By contrast, responses to the motion stimulus were not correlated across light levels in either group (see Figure 6.3, top right & bottom left). This

indicates that in both groups, topographies during form processing, but not motion processing, remained consistent across the transition from mesopic to scotopic light levels.

In comparisons of form vs motion topographies at matching light levels (Figure 6.2, right), responses to the two kinds of stimulus were significantly correlated in both control and stationary groups in scotopic light. By contrast, in mesopic light, only the stationary group showed significantly correlated form vs motion topographies. This indicates that there are significant commonalities in topographies during processing of form and motion stimuli, which break down only in the case of controls under mesopic viewing. The lack of correlation in the mesopic condition was not only due to a weak signal in one or both conditions, as can be seen in Figure 6.3 (bottom right plot).

To summarise, the correlations show that (1) typical form topographies, but not motion topographies, were preserved in the stationary group; (2) in both groups, topographies during form (but not motion) processing were consistent across mesopic and scotopic levels; (3) processing of form and motion stimuli led to correlated topographies, except for controls in mesopic light.

6.3.3 VEP Amplitude - Regions of Interest

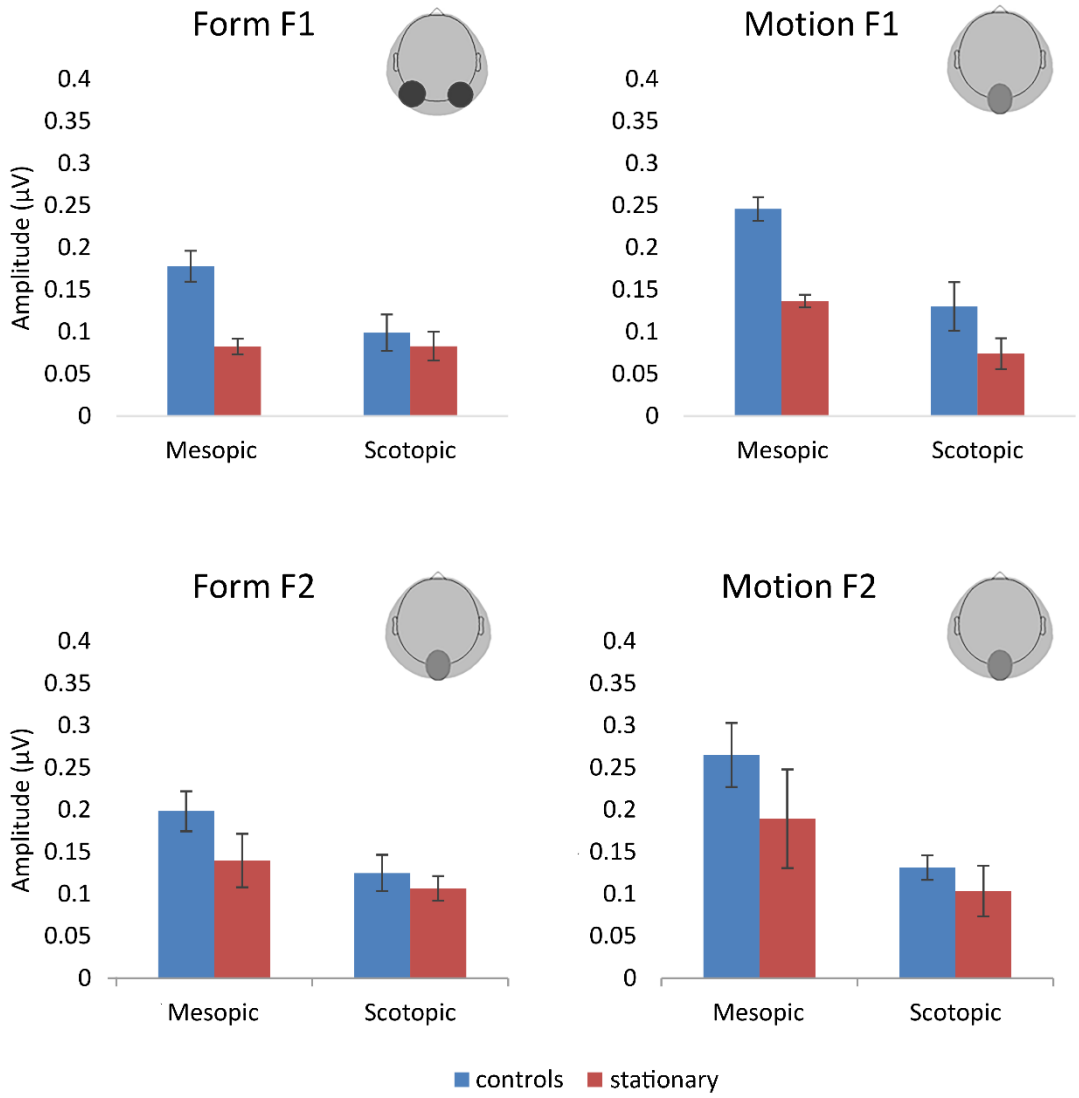

Figure 6.4. F1 (top) and F2 (bottom) form and motion VEP amplitudes (μV) taken from a region of interest (ROI). Amplitudes were averaged across electrodes within the ROI for each participant and group means were then calculated. Error bars represent the standard error of the mean.

The preceding analysis of correlations across topographies does not address the issue of overall amplitude of response, as patterns of activation can be correlated but have a lower base level in one group. To determine whether amplitudes were different, mean amplitudes

were taken from a cluster of electrodes identified as most active in the control group in mesopic conditions. These regions of interest (ROIs) are shown above the form and motion plots in Figure 6.4.

As can be seen in Figure 6.4, F1 VEP amplitudes were reduced in the stationary group compared to controls for both form and motion. A repeated measures ANOVA comparing controls and stationary patients found a main effect of test ($F(1,27) = 4.391$, $p = 0.046$), with responses higher for motion than for form; light ($F(1,27) = 20.540$, $p < 0.001$), with responses higher at mesopic than scotopic levels; and group ($F(1,27) = 12.225$, $p = 0.002$) with responses higher in the control group. There was also a significant light x group interaction ($F(1,27) = 5.476$, $p = 0.027$) indicating the stationary patients and controls were differentially affected by light levels. As Figure 6.4 shows, for both form and motion, F1 amplitudes were more reduced in scotopic (as compared with mesopic) conditions for controls than for stationary patients.

Patient and control F2 amplitudes showed a main effect of light ($F(1,24) = 24.540$, $p<0.001$) with responses higher at mesopic than scotopic levels, but no main effect of test ($F(1,24) = 2.818$, $p = 0.106$) or light x group interaction ($F(1,24) = 0.260$, $p = 0.146$) indicating the stationary patients and controls were similarly affected by light levels. Unlike F1 amplitudes, there was no significant effect of group ($F(1,24) = 1.139$, $p = 0.297$) which suggests that stationary patients and controls were similarly affected across tests and light levels.

6.4 DISCUSSION

Coherent form and motion SSVEP tests were carried out with stationary (ACHM) patients to assess whether they had different patterns or amplitudes of cortical activation relative to controls. Topographic plots showed that F1 responses, sensitive to stimulus coherence, varied between patients and controls with patient responses generally weaker and less clear. F2 responses, sensitive to local changes were comparable between the two groups. For the form stimulus these F2 responses were localised to the occipital midline. Motion F2 responses were also located over the occipital midline in mesopic conditions but minimal responses were seen for both groups in the scotopic condition.

Correlational analyses of F1 amplitudes taken from all scalp electrodes revealed further consistencies and discrepancies between the two groups. Responses to coherent form stimuli were significantly correlated between patient and control groups in both mesopic and scotopic conditions. Responses to coherent motion, however, were not significantly correlated between groups in mesopic conditions and were negatively correlated in scotopic conditions. The result that form responses but not motion responses showed similarities in topography between patients and controls suggests there may be different neural substrates for coherent motion (but not form) processing in the patients. It may be that form processing uses the same network in patients as in controls while for motion processing a different network is used. Lack of correlation in motion topographies was not explained simply by a weak response in the patient group. Importantly, the correlated topography for form in patients and controls does not imply “normal” cortical processing of coherent form, as the subsequent analysis of amplitudes showed these to be reduced in the patient group.

Mean amplitudes of responses to coherent form and motion stimuli at the two light levels were analysed in specific regions of interest. Patients had reduced F1 form and motion amplitudes relative to controls but comparable F2 amplitudes. These reductions in amplitude

are consistent with behavioural results of reduced mean perceptual sensitivity to coherence for both kinds of stimuli (chapter 5). F1 amplitudes also showed a different effect of light in controls and patients, with controls showing a greater reduction in amplitude from mesopic to scotopic levels than the patients. This is also in line with behavioural results (chapter 5), in which controls' performance deteriorated more markedly at lower light levels, consistent with loss of the additional cone signal at low light in controls, but not patients. SSVEP results did not show significant differential impairments across the two tests, form and motion (i.e. any interactions involving group and test). However, the stimulus which showed most striking dissociations from the others behaviourally, biological motion, was not included here as it did not provide measurable SSVEP responses in controls or patients.

The results suggest that similar neural substrates may be underlying form perception in the controls and patients but not motion perception. Patients' processing of these stimuli is not at normal levels, however, as amplitudes of responses to both are reduced. Exactly what underlies differences between patients and controls in coherent motion F1 topographies remains unclear. Most striking is the significant negative correlation in patient vs. control motion topographies in scotopic light, where controls show a mid-right occipital peak (Fig. 1, bottom row, first plot), while patients show very little activation in the same region but some more frontal activation (Fig. 1, bottom row, second plot) that is absent in controls.

It is of interest that patients showed greater impairments on form tests than motion tests in the behavioural chapter (chapter 5). It may be that the shift in activation seen in patients' motion topography represents a developmental specialisation that allows for better motion perception when vision is impaired. While no other imaging studies investigating coherent motion perception in ACHM have been carried out, related work has been carried out with amblyopia. Interestingly, an fMRI study demonstrated atypical neural activation when patients viewed coherent motion through their amblyopic eye compared to controls, an effect which was not seen when patients viewed the stimulus through their non-amblyopic eye

(Thompson, Villeneuve, Casanova, & Hess, 2012). Amblyopic patients had previously demonstrated normal coherent motion perception on behavioural tasks when tested using their amblyopic eye (Thompson, Aaen-Stockdale, Mansouri, & Hess, 2008). As with our findings, these results suggest that when vision is impaired, there is a change in neural activation which is associated with a relative preservation of coherent motion perception.

The correlational analysis also revealed that form responses remained consistent in topography across mesopic and scotopic conditions for both groups. Motion results, however did not correlate with each other across mesopic and scotopic conditions in patients or controls. This suggests that the form VEP responses were generated by similar brain regions in mesopic and scotopic conditions while motion VEP responses were generated by different regions. Patients and controls were consistent in this finding and both therefore appear to be shifting their pattern of activation to motion responses in low light. As with the finding that patients show different motion responses to controls, the shift in motion topography in low light may be further evidence that different brain regions are activated in response to coherent motion when vision is limited. As with the amblyopic patients described previously (Thompson et al., 2012), low light presents a situation in which visual input is impaired relative to brighter conditions.

The finding that F2 amplitudes were not significantly different between patients and controls suggests that processing of local elements of coherent form and motion stimuli may be similar between the two groups. This is also reflected in the topographic plots which show similar regions and intensities of activation. These results therefore suggest specific changes in global processing (F1) rather than local processing (F2). One reason the F1 amplitudes may have shown differences between patients and controls may lie in the ROIs used. These were selected based on the control group data, however the topographic plots and correlational analyses suggest that in some cases patient topography differed from controls. The ROIs may not therefore represent the areas of peak activation in the patients. Given the

small group size, it was not possible to select a clear peak ROI in the patient group. However, these results indicate interesting differences between the patients and controls in both form and motion processing.

The brain regions underlying coherent form and motion perception in ACHM patients remains elusive. Further work using imaging techniques with better spatial resolution such as source localisation or fMRI would allow for a greater understanding of how neural activity may differ from normal in ACHM. These results provide important insight into the fact that the neural activation in ACHM differs from controls, especially in the case of coherent motion perception.

CHAPTER 7. DISCUSSION

6.5 RESEARCH AIMS

The work within this thesis aimed to understand how mid-level vision is affected in cases of visual deprivation, specifically deprivation of cone input to the visual system. This was achieved by comparing normally sighted controls to patients with cone disorders on three tests of visual perception – coherent form, coherent motion and biological motion. It is hoped that a thorough understanding of vision in these patients will allow us to understand the role of specific photoreceptor pathways in the function and development of mid-level vision as well as providing important baseline information that can be taken forward for future use in clinical trials of new therapies.

6.6 SUMMARY OF RESEARCH FINDINGS

No previous work into mid-level visual function in patients with cone disorders had been carried out. A summary of the findings within this thesis will be outlined below, followed by discussion of conclusions drawn from across chapters.

Chapter 3 explored how mid-level vision in normally sighted controls is affected by blur. This aimed to understand how coherent form, motion and biological motion are impaired by the loss of high spatial frequencies. The 20 participants in this study had normal vision and as such their results under blur can inform us of how visual processing in the healthy visual system changes when there is a loss of high spatial frequencies. These participants were therefore free from long-term adaptations which may be present in patient populations. However, results from this approach have the potential to help with the interpretation of mid-level vision results in groups who also have loss of high spatial frequencies - including not only patients with cone disorders, but other groups with visual impairments such as amblyopia and also typically and atypically developing infants and children, who have reduced acuity and contrast sensitivity compared to normal adults. Changes following loss of high spatial frequencies in controls provide a starting point for determining whether there are atypicalities of mid-level visual processing in a patient group that are over and above those expected simply from high spatial frequency loss.

Results showed that perceptual sensitivity to coherent form and motion were impaired by blur, but perception of biological motion was not impaired at the highest level of blur tested (equivalent to an acuity of 1.2 LogMAR). Coherent form sensitivity was particularly affected relative to motion. VEP amplitudes were reduced by blur for global form and motion, although in this case no difference was seen in the degree of amplitude change for the two tests.

The results of chapter 3 suggest that good acuity and contrast sensitivity are important in the perception of coherent form and, to a degree, for coherent motion but not for biological motion. Results were in keeping with findings that coherent motion perception under blur is more robust than coherent form perception (Zwicker, Hoag, Edwards, Boden, & Giaschi, 2006). Differences in the visual pathways which process form and motion may have contributed to these findings. Form perception is more reliant on processing in the ventral stream while motion perception depends more on the dorsal stream. Input to these two streams is dependent largely, although not exclusively, on parvocellular neurons projecting to the ventral stream and magnocellular to the dorsal. Differences in the preference of these input streams to high or low spatial frequencies, and in their sensitivity to motion, is therefore likely to indirectly affect coherent form and motion perception. This result is in contrast to findings with other patient and developmental groups (e.g. Atkinson & Braddick, 2011; Atkinson et al., 1997, 2004; Braddick, Atkinson, & Wattam-Bell, 2003) who have generally demonstrated greater impairments on dorsal-mediated tasks relative to ventral. 6-8 year-old typically developing children have acuity and contrast sensitivity very close if not at adult levels and yet they still show considerably reduced motion coherence sensitivity compared to adults. The difference between these results and those seen in chapter 3 suggest that impairments in patients and developmental populations are not simply the result of low level impairments in acuity and/or contrast sensitivity.

Chapter 4 looked at how perception of coherent form, motion and biological motion is affected by changes in luminance in controls with healthy vision. These results were important in providing baseline measures of visual perception under low light which could later be compared to patient populations to investigate how cone disorders affect mid-level perception.

Results on the behavioural tests showed that while performance on all three coherence measures (form, rotary motion and biological motion) was impaired by low light, coherent

form perception showed a greater impairment than either of the motion tests. This result was somewhat similar to the findings of the blur study and is likely to be due to the spatial frequency information available in different light conditions. In low light, vision is restricted to low spatial frequencies due to a reliance on rod photoreceptors, whose high convergence ratio with ganglion cells does not allow the rod pathway to sample high spatial frequencies. Coherent motion and biological motion perception are able to continue to function more efficiently than coherent form when high spatial frequencies are absent.

In contrast with blur results in chapter 3, which found biological motion perception to be unimpaired by even relatively high blur, it was impaired under low light. This may indicate the limitations of temporal perception associated with rod vision. Under diffuser blur, vision was mediated by cones which have excellent temporal resolution. However, vision in scotopic conditions is mediated by rods which have poor temporal resolution relative to cones. Impairments seen in low light relative to blur for biological motion perception are likely to reflect the loss of precise temporal information.

Controls' VEP results in scotopic conditions, also reported in chapter 4, found a topographical reorganisation of global motion but not global form when compared to mesopic conditions. This may indicate a mechanism by which global motion is able to continue functioning in low light. Any changes in neural substrates underlying this topographical shift remain unclear and further work would be required to understand these changes in neural activation.

Chapter 5 compared the behavioural baseline results of controls in chapter 4 to those collected with patients with stationary and progressive cone disorders. These measures were intended to provide insight into how mid-level vision is affected in those with congenital stationary cone disorders and those with later-onset progressive cone dystrophies.

Results found that patients with a congenital stationary cone disorder (ACHM) had, on average, impairments on tests of coherent form and motion at all light levels. This included scotopic conditions, in which patients and controls are in theory matched in the sense that both must rely on rods. Biological motion perception however was not impaired in these patients under scotopic conditions. CSF results revealed variation in patients' low-level scotopic sensitivity, with the majority showing low-level impairments. The results suggests that ACHM patients may have become specialised to be able to perceive biological motion successfully despite the limitations of rod mediated vision.

Patients with progressive cone disorders were worse than controls on all three tests. This was true in both photopic and scotopic conditions. CSF results found that the majority of progressive patients (4/5) had low-level impairments in their scotopic vision, suggesting additional loss of rod function. The one patient with normal scotopic sensitivity remained impaired on tests of coherent form and biological motion suggesting that despite low-level vision being matched to controls, this patient had deficits in mid-level visual perception.

Chapter 6 compared the stationary patients to controls on EEG tests of coherent form and motion perception. Results found reduced amplitudes for form and motion perception in patients compared to controls, especially in brighter light conditions, which is consistent with their reduced perceptual sensitivity. Correlational analyses suggested that motion topography was atypical relative to controls whereas form perception was similar to controls but of reduced amplitude. This may indicate potential mechanisms by which motion perception is relatively spared in these patients relative to form perception and different cortical networks for motion relative to form.

6.7 EVIDENCE OF PLASTICITY

One of the aims of this thesis was to identify whether an absence of cone-mediated vision could lead to changes in mid-level visual perception which are not simply explained by low-level visual deficits. Any atypicalities seen in patients which could not be explained by their low-level impairments could be suggestive of specific impairments or adaptations of mid-level vision which have come about due to cone-specific deprivation.

The ability to perceive coherent form, motion and biological motion perception is known to be shaped by experience. Developmental studies have demonstrated long developmental trajectories of coherent form, motion and biological motion perception (Atkinson et al., 2004; Atkinson and Braddick,2005; Braddick et al., 2003, Freire, Lewis, Maurer, & Blake, 2006; Gunn et al ,2002; Kiorpes, Price, Hall-Haro, & Movshon, 2012; Lewis et al., 2004; Norcia et al., 2005). These trajectories reflect more than just the maturation of neural networks within the cortex as they are known to be affected by visual deprivation, highlighting the need for visual experience in their development.

Studies of patients who have undergone visual deprivation have found that a loss of vision in the first year of life can have long-term implications for the perception of coherent form and motion (Ellemberg, Lewis, Maurer, Brar, & Brent, 2002; Hadad, Maurer, & Lewis, 2011; Lewis et al., 2002). For example in children treated for binocular cataracts long term impairments have been observed in coherent form and motion perception (Ellemberg et al., 2002; Lewis et al., 2002). The question of how biological motion perception is affected by deprivation is less clear. Studies with cataract and amblyopia patients have reported normal biological motion perception despite considerable periods of visual deprivation (Hadad, Maurer, & Lewis, 2012; Neri, Luu, & Levi, 2007). This suggests that biological motion perception is able to develop without patterned visual input in infancy. However, it remains unclear to what degree visual experience is needed for biological motion perception and

whether longer-term impairments than those seen in infant cataract patients would lead to impairments.

Studying patients with cone disorders allowed a specific type of visual deprivation to be investigated – deprivation due to loss of cone photoreceptors. By studying patients who have lived without cones throughout their lives (ACHM patients) it is possible to gain an understanding on how coherent form, motion and biological motion perception may have developed in these patients. Furthermore, comparison between controls and patients with progressive cone disorders provides insight into how late-onset loss of cone function may impact on these types of visual perception.

The finding that coherent form and motion perception are impaired in patients with cone disorders is largely in agreement with previous studies of infant cataract patients. However, in the case of cataract patients, vision was restored following cataract removal, usually within the first year. Changes in these patients therefore represent those which have come about due to early vision loss during critical periods of visual development. In our patient groups, visual deprivation of cone input is long-term and any impairments are the result of not only vision loss during early critical periods but also during later childhood and adult life. This may have further impact on mid-level visual function as it is known that coherent form, motion and biological motion all continue to develop well into childhood (Atkinson et al., 2004; Braddick et al., 2003;Gunn et al , 2002; Hadad et al., 2011). However, the patients in the present studies also differ from the cataracts patients in that they have had consistent visual input, albeit of low acuity and contrast sensitivity, in the form of rod-mediated vision.

Of particular interest in these studies was whether patients continued to show impairments in mid-level vision even if their low-level vision was comparable to controls. Any such impairments under these conditions must be attributable to changes to mid-level vision which have come about due to long-term cone-loss rather than to low-level impairments. In

an attempt to match patients' and controls' mid-level vision, all participants were tested under scotopic conditions. Previous research had suggested that scotopic low-level vision in ACHM was comparable to controls indicating normal rod functioning (Hess & Nordby, 1986a, 1986b; Sloan & Feiock, 1972). However, our findings indicated this was not the case in the patients we studied. The majority of ACHM (6/9) and PCD (4/5) patients had low-level impairments as indicated by the CSF test. Recent findings with ACHM patients have suggested that in some individuals rod sensitivity may not be optimal (Aboshiha et al., 2014; Sundaram et al., 2014). Our study confirms this finding and adds weight to the idea that individual variations in rod sensitivity exist in these patients. Results suggest that patients and controls were not, on the whole, matched under scotopic conditions.

However, 3/9 ACHM patients did show normal scotopic CSF results and these patients were therefore focussed on for further analyses. If these patients showed scotopic coherent form, motion and biological motion perception comparable to controls, it would indicate that these visual skills had developed normally. In fact, the three patients with normal scotopic sensitivity showed some deviation from the control group in their mid-level perception. 2/3 had scotopic impairments on coherent form while 2/3 were superior to controls on biological motion tests. Coherent motion perception was comparable to controls in these three patients. These results suggest that rod-mediated vision alone is insufficient for development and functioning of coherent form perception. Coherent motion and biological motion perception however, had developed to a level comparable to controls or better in these patients indicating that rod-mediated vision is sufficient for development of these abilites.

The results seen in these patients are opposite to those seen in other low-vision and developmental populations who have consistently been reported to demonstrate greater impairment in motion perception over form (Atkinson & Braddick, 2011; Atkinson et al., 1997, 2004). These results have been ascribed to dorsal stream vulnerability in which the dorsal stream is more vulnerable to disruption than the ventral stream (Atkinson & Braddick, 2011).

However, the patients described here have a very particular type of visual impairment in which rod vision is present from birth.

The finding that biological motion perception was superior to controls in 2/3 patients was of interest and supports the idea that this type of perception can develop and function without high spatial or temporal frequencies. These results mirror those seen in patients with congenital cataracts and amblyopia. Possible reasons behind the biological motion findings may lie in the adaptability of neural networks within the visual cortex which contribute to the perception of biological motion. While biological motion is thought to be dependent on both ventral and dorsal visual streams (Giese & Poggio, 2003), providing structural information about the biological form of the figure as well as motion cues, there is evidence from patients with damage to the visual cortex that suggests that biological motion is robust against loss of either one of these pathways (Gilaie-Dotan, Bentin, Harel, Rees, & Saygin, 2011; McLeod, Dittrich, Driver, Perret, & Zihl, 1996; Vaina, Lemay, Bienfang, Choi, & Nakayama, 1990). If cone disorder patients have reduced ventral stream processing, as their form impairments suggest, it may be that these patients have adapted over time to rely more heavily on motion signals in the perception of biological motion.

The biological motion task differed from the form and motion tasks in the way in which coherence varied. For the form and motion tasks, dot density remained consistent at each level of coherence. The biological motion task varied in dot density depending on the degree of noise present, because the noise level was manipulated by adding more (noise) dots. This difference in task design may have led to differences in the way the two tasks were perceived and how performance was affected by blur, low light, or ACHM. Following up these results with a range of other kinds of biological motion stimuli would be useful. However, it is not clear how the way in which these particular stimuli were presented could explain the relative advantage for biological motion as compared with the other stimuli in the case of blur or ACHM. The increase in dot density with increasing noise should if anything

tend to make this task progressively more difficult at high noise levels, compared with the fixed-density motion and form tasks. In addition, to account for possible differences in difficulty across tasks, any comparisons made between the tasks used z-scores to normalise data to a baseline level.

The findings on biological motion perception seen here may be related to reports by Sacks (Sacks, 1996) that the achromatopsia population on the Pingalpese atoll report enhanced night fishing abilities. The ability to detect shoals of fish seen in these patients would involve the processing of complex motion signals. Exactly how this skill may be related to the findings of enhanced biological motion perception remains elusive but provides interesting scope for future research.

Within the PCD group only one patient had scotopic low-level vision (i.e. a CSF) comparable to controls, suggesting there may be suboptimal rod functioning in the majority of this group and again highlighting the variability seen between patients with cone disorders. While it is hard to draw conclusions regarding just one patient it was of interest that this patient did not share the advantage of spared biological motion perception seen in the ACHM patients. He was in fact worse at tests of coherent form and biological motion despite being matched to controls in their low level vision. Only coherent motion perception was comparable to the control group. These results may indicate changes that occur to mid-level vision following deprivation in later-life as this patient only lost their cone function in late adolescence, after coherent form, motion and biological motion perception are believed to have fully developed. It therefore appears that some aspects of mid-level vision not only suffers during critical periods of visual development but may also be dependent on good visual input to continue functioning normally.

6.8 IMPLICATIONS FOR THERAPY

One of the long-term aims of these tests was for them to be used in clinical trials of new therapies for cone disorders. Never before have tests of mid-level function been used to assess visual outcome following gene or stem cell therapy. Use in future trials will allow exciting insights into the plasticity of mid-level vision in these patients.

The success of new therapies in cone disorder patients will rely on their visual systems adapting to new visual input. Previous studies have provided mixed results on the visual system's ability to adapt to new visual input. Studies of cataract patients have found long-term impairments in many aspects of visual perception including coherent form and motion perception years after cataract removal (Ellemberg et al., 2002; Lewis et al., 2002). However, recent work into amblyopia has suggested that some aspects of visual performance, such as stereoacuity, can improve into adulthood given the right environmental factors (Astle, McGraw, & Webb, 2011; Holmes et al., 2011), and that therapeutic interventions may be possible into adulthood (Levi & Li, 2009; Li et al., 2015; Vedamurthy et al., 2015). This ongoing work on conditions underlying plasticity of the developed visual system has the potential to inform new therapeutic approaches to retinal disease.

The finding that scotopic coherent motion and biological motion perception are normal in ACHM patients with normal scotopic vision suggests that the neural networks involved in their perception have developed to be able to process the rod input as well as those of normally sighted controls. Like controls in scotopic conditions, ACHM patients are limited by the restricted low-level input received by rod-only vision, but otherwise their scotopic vision is normal (for biological motion) or near-normal (for motion). However, it is unknown to what extent patients provided with a new cone signal (e.g. via gene replacement therapy) would also show improvements in mesopic and photopic mid-level vision, in line with controls' better sensitivity in these conditions. It could be that the networks are in place and all that is

needed is enhanced visual input in brighter conditions, provided by cones. Conversely, it may be that neural networks involved in the perception of coherent motion and in particular biological motion have developed atypically, for example being biased to receive most or all of their input from rods and the magnocellular stream. If this is the case, adaptation may be more difficult following therapy as networks will have already specialised to deal with rod input.

6.9 FUTURE DIRECTIONS

The studies described here had some limitations and addressing some of these will provide the first step in any future research. In addition, this research has presented many more questions than it was possible to address within this thesis and future work would aim to further understanding in this area by addressing some of these.

One of the key problems when dealing with rare medical conditions is the issue of small group sizes. This can make it hard to draw firm conclusions regarding the population being studied. In the case of ACHM, participants were limited by the low prevalence of the condition. This was even more apparent for PCD which is very rare and represents a cluster of different conditions. Future work could aim to recruit more patients to try to identify whether the patterns seen here are representative of ACHM and PCD as a whole. It would be of relevance to address whether the variability seen in low-level vision was true of larger group sizes

The finding that ACHM does not produce a uniform phenotype in scotopic conditions indicates variability in rod function in this patient group. The exact reasons behind this remain elusive and it would be of interest to address this further in future work. Existing studies of rod sensitivity in ACHM are few (Aboshiha et al., 2014; Hess & Nordby, 1986a, 1986b; Sloan & Feiock, 1972; Sundaram et al., 2014) and are mixed in their reports of typical and atypical scotopic sensitivity in achromatopsia. However, those that indicate variability between patients (Aboshiha et al., 2014; Sundaram et al., 2014) report that this does not appear accountable to genotype or age. Identifying what is responsible for the variation seen in these patients may be important in identifying who will benefit most from future therapies. For example, gene therapy being developed for ACHM focusses on correcting cone deficits, and this may be of most success in patients who already demonstrate healthy rod functioning.

Another issue with the tests used in this thesis is that although they are excellent at probing mid-level vision in an experimental setting, they are not directly applicable to real world situations, therefore the conclusions which can be drawn from them are limited. The coherent form, motion and biological motion tests used within this thesis have been designed to allow maximum control over experimental parameters to allow the detection of subtle differences between participants. However, they do not allow us to understand how a person may perceive in the real world. In a real-world setting people use a combination of form and motion to perceive their surroundings.

More natural tasks with these patients would complement the experiments seen within this thesis. It would be of interest to see if the form deficits seen in cone disorder patients translate into problems with object recognition and whether form and motion deficits affect these patients' ability to navigate in the world. The perception of optic flow (a type of coherent motion perception) is important for self-motion, while form perception is used to navigate with landmarks. A battery of visuo-spatial tasks, carried out in a range of light levels including scotopic, could be used to test patients using more naturalistic tasks. This could include tasks such as catching a ball, recognising and manipulating everyday objects, and navigating through an environment.

As well as these more natural tasks it would be of interest to further probe other types of mid-and high-level vision in these patients to see how far these deficits, (and in some cases of biological motion perception, advantages) extend. A test of form-from-motion would be of particular interest for the ACHM patients given their normal biological motion but impaired form perception. Form-from motion probes a person's ability to detect a moving form. This is usually tested by presenting a group of coherent dots which together make up a shape, presented against an incoherently moving background. As with the biological motion test participants must extract and integrate motion cues in order to see a form. Testing ACHM

patients on this test would allow us to see whether their normal biological motion perception is specific to something biological regarding the stimulus.

Another future direction would be the testing of younger participants. One of the questions raised in this thesis was whether the results seen in ACHM are the result of atypical visual development. However, any inferences made about this are indirect as patients were all adults and the degree to which their results came about due to changes in early development as opposed to later life are unclear. Testing ACHM patients on coherent form, motion and biological motion perception across a range of ages would allow insight into how performance on these tests change with age as well as how patients compare to age-matched controls at different points during development. Ideally this would be performed with a longitudinal design which would cancel out the effects of individual variation we have observed in these patients.

The use of EEG in this thesis provided interesting insight into the neural activity underlying coherent form and motion perception. However, its use is limited in that it cannot provide us with precise information about the underlying brain structures associated with the differences observed between patients and controls. Using additional neuroimaging techniques with these patients such as fMRI (or source-localised EEG, ideally in conjunction with structural MRI scans) would allow further understanding of where and how patients' cortical activity differs when performing coherent form and motion tests. Developing a suitable way to measure neural activity during biological motion processing, which was not possible here, would also provide important insight into the domain in which patients showed some of the most interesting results. fMRI and TMS of coherent form, motion and biological motion has already been carried out in visually normal groups (Braddick, O'Brien, Wattam-Bell, Atkinson, & Turner, 2000; Braddick et al., 2001; Grossman & Blake, 2002; Harvey, Braddick, & Cowey, 2010; Peelen, Wiggett, & Downing, 2006) and opens the possibility of gaining greater understanding of the neural activity of these patients.

6.10 CONCLUSIONS

The perception of coherent form, motion and biological motion relies on complex neural networks, formed early in life. While previous work had shown that these networks are vulnerable to disruption in some visually impaired and developmental populations, no work had previously been carried out in populations with retinal disorders. By studying patients with cone disorders, it has been possible to examine, for the first time, how an absence of cones impacts on mid-level vision. The finding that patients with a congenital absence of cones show impairments in their photopic mid-level processing is as expected, however findings in scotopic conditions, particularly in patients who demonstrate normal low-level perception has shed light on specific vulnerabilities and resilience in mid-level perception in these patients. These results provide important baseline information on mid-level vision which can be used in future trials of new therapies and will allow the impact of vision restoration on mid-level vision to be investigated.

REFERENCES

Aboshiha, J., Dubis, A. M., Carroll, J., Hardcastle, A. J., & Michaelides, M. (2015). The cone dysfunction syndromes. *British Journal of Ophthalmology*, *88*(2), 291–297. http://doi.org/10.1136/bjophthalmol-2014-306505

Aboshiha, J., Dubis, A. M., Cowing, J., Fahy, R. T. A., Sundaram, V., Bainbridge, J. W., Ali, R. R., Dubra, A., Nardini. m., Webster. A. R., Moore, A. T., Rubin. G., Carroll, J., & Michaelides, M. (2014). A Prospective Longitudinal Study of Retinal Structure and Function in Achromatopsia. *Investigative Ophthalmology & Visual Science*, *55*(9), 5733–5743. http://doi.org/10.1167/iovs.14-14937

Aboshiha, J., Luong, V., Cowing, J., Dubis, A. M., Bainbridge, J. W., Ali, R. R., Webster, A. R., Moore, A. T., Fitzke, F. W., & Michaelides, M. (2014). Dark-Adaptation Functions in Molecularly Confirmed Achromatopsia and the Implications for Assessment in Retinal Therapy Trials. *Investigative Ophthalmology & Visual Science*, *55*(10), 6340.

Adrian, E. D., & Matthews, B. H. C. (1934). The interpretation of potential waves in the cortex. *The Journal of Physiology*, *81*(4), 440–471. http://doi.org/10.1113/jphysiol.1934.sp003147

Ahlstrom, V., Blake, R., & Ahlstrom, U. (1997). Perception of biological motion. *Perception*, *26*(12), 1539-1548.

Ales, J. M., Farzin, F., Rossion, B., & Norcia, A. M. (2012). An objective method for measuring face detection thresholds using the sweep steady-state visual evoked response. *Journal of Vision*, *12*(10). http://doi.org/10.1167/12.10.18

Angelelli, P., de Luca, M., & Spinelli, D. (1996). Early visual processing in neglect patients: a study with steady-state VEPs. *Neuropsychologia*, *34*(12), 1151–1157.

Astle, A. T., McGraw, P. V., & Webb, B. S. (2011). Can Human Amblyopia be Treated in Adulthood? *Strabismus*, *19*(3), 99–109. http://doi.org/10.3109/09273972.2011.600420

Atkinson, J, & Braddick, O. (2005). Dorsal stream vulnerability and autistic disorders: the importance of comparative studies of form and motion coherence in typically developing children and children with developmental disorders. *Cahiers de Psychologie Cognitive*, *23*(1-2), 49–58.

Atkinson, J, Wattam-Bell, J., Braddick, O., Birtles, D., Barnett, A., & Cowie, D. (2004). Form vs motion coherence sensitivity in infants: the dorsal/ventral developmental debate continues. *Journal of Vision*, *4*(8), 32–32. http://doi.org/10.1167/4.8.32

Atkinson, J., & Braddick, O. (2007). Visual and visuocognitive development in children born very prematurely. *Progress in Brain Research*, *164*, 123.

Atkinson, J., & Braddick, O. (2011). From genes to brain development to phenotypic behavior:“ dorsal-stream vulnerability” in relation to spatial cognition, attention, and planning of actions in Williams syndrome (WS) and other developmental disorders. *Progress in Brain Research*, *189*, 261.

Atkinson, J., King, J., Braddick, O., Nokes, L., Anker, S., & Braddick, F. (1997). A specific deficit of dorsal stream function in Williams' syndrome. *Neuroreport*, *8*(8), 1919–1922.

Atkinson, Janette, Braddick, O., Anker, S., Curran, W., Andrew, R., Wattam-Bell, J., & Braddick, F. (2003). Neurobiological models of visuospatial cognition in children with Williams syndrome: measures of dorsal-stream and frontal function. *Developmental Neuropsychology*, *23*(1-2), 139–172.

Baker, C. I., Dilks, D. D., Peli, E., & Kanwisher, N. (2008). Reorganization of visual processing in macular degeneration: Replication and clues about the role of foveal loss. *Vision Research*, *48*(18), 1910–1919. http://doi.org/10.1016/j.visres.2008.05.020

Baker, C. I., Peli, E., Knouf, N., & Kanwisher, N. G. (2005). Reorganization of visual processing in macular degeneration. *The Journal of Neuroscience*, *25*(3), 614–618.

Banin, E., Gootwine, E., Obolensky, A., Ezra-Elia, R., Ejzenberg, A., Zelinger, L., Honig, H., Rosov, A., Yamin, E., Sharon, D., Averbukh, E., Hauswirth. W. W., & Ofri. R. (2015). Gene Augmentation Therapy Restores Retinal Function and Visual Behavior in a Sheep Model of CNGA3 Achromatopsia. *Molecular Therapy*, *23*(9), 1423-1433.

Bardi, L., Regolin, L., & Simion, F. (2011). Biological motion preference in humans at birth: Role of dynamic and configural properties. *Developmental Science*, *14*(2), 353–359.

Barlow, H. B. (1962). Measurements of the quantum efficiency of discrimination in human scotopic vision. *The Journal of Physiology*, *160*(1), 169–188.

Barten, P. (1999). Chapter 3: Models for the spatial contrast sensitivity of the eye. In *Contrast Sensitivity of the Human Eye and Its Effects on Image Quality*. (p. 44) Bellingham, WA: SPIE Press.

Barton, J. J. S., Rizzo, M., Nawtrot, M., & Simpson, T. (1996). Optical Blur and the Perception of Global Coherent Motion in Random Dot Cinematograms. *Vision Research*, *36*(19), 3051–3059. http://doi.org/10.1016/0042-6989(96)00063-6

Baseler, H. A., Brewer, A. A., Sharpe, L. T., Morland, A. B., Jagle, H., & Wandell, B. A. (2002). Reorganization of human cortical maps caused by inherited photoreceptor abnormalities. *Nature Neuroscience*, *5*(4), 364–370.

Baseler, Heidi A., Gouws, A., Haak, K. V., Racey, C., Crossland, M. D., Tufail, A., Rubin, G. S., Cornelissen. F. W., & Morland, A. B. (2011). Large-scale remapping of visual cortex is absent in adult humans with macular degeneration. *Nature Neuroscience*, *14*(5), 649–655. http://doi.org/10.1038/nn.2793

Baseler, Heidi A., Gouws, A., & Morland, A. B. (2009). The organization of the visual cortex in patients with scotomata resulting from lesions of the central retina. *Neuro-Ophthalmology*, *33*(3), 149–157.

Beintema, J. A., & Lappe, M. (2002). Perception of biological motion without local image motion. *Proceedings of the National Academy of Sciences*, *99*(8), 5661–5663.

Benedek, G., Benedek, K., Kéri, S., Letoha, T., & Janáky, M. (2003). Human scotopic spatiotemporal sensitivity: a comparison of psychophysical and electrophysiological data. *Documenta Ophthalmologica*, *106*(2), 201–207. http://doi.org/10.1023/A:1022548013313

Benjamini, Y., & Hochberg, Y. (1995). Controlling the false discovery rate: a practical and powerful approach to multiple testing. *Journal of the Royal Statistical Society. Series B (Methodological)*, 289–300.

Berman, N., & Daw, N. W. (1977). Comparison of the critical periods for monocular and directional deprivation in cats. *The Journal of Physiology*, *265*(1), 249–259.

Bertenthal, B. I., Proffitt, D. R., & Cutting, J. E. (1984). Infant sensitivity to figural coherence in biomechanical motions. *Journal of Experimental Child Psychology*, *37*(2), 213–230.

Besharse, J., & Bok, D. (2011). *The Retina and its Disorders*. Academic Press.

Billino, J., Bremmer, F., & Gegenfurtner, K. R. (2008). Motion processing at low light levels: Differential effects on the perception of specific motion types. *Journal of Vision*, *8*(3), 14, 1-10.

Birch, E. E., Stager, D., Leffler, J., & Weakley, D. (1998). Early treatment of congenital unilateral cataract minimizes unequal competition. *Investigative Ophthalmology & Visual Science*, *39*(9), 1560–1566.

Birch, E. E., & Stager, D. R. (1988). Prevalence of good visual acuity following surgery for congenital unilateral cataract. *Archives of Ophthalmology*, *106*(1), 40.

Blake, R., Turner, L. M., Smoski, M. J., Pozdol, S. L., & Stone, W. L. (2003). Visual recognition of biological motion is impaired in children with autism. *Psychological Science*, *14*(2), 151–157.

Blakemore, C., & Cooper, G. F. (1970). Development of the brain depends on the visual environment. *Nature, 228*(5270), 477-478.

Blakemore, C., & Sluyters, R. C. V. (1974). Reversal of the physiological effects of monocular deprivation in kittens: further evidence for a sensitive period. *The Journal of Physiology*, *237*(1), 195–216.

Bonda, E., Petrides, M., Ostry, D., & Evans, A. (1996). Specific involvement of human parietal systems and the amygdala in the perception of biological motion. *The Journal of Neuroscience*, *16*(11), 3737–3744.

Boothe, R. G. (2006). *Perception of the Visual Environment*. Netherlands: Springer Science & Business Media.

Braddick, O., Akthar, F., Anker, S., & Atkinson, J. (2007). Global form and global motion sensitivity are equally resistant to blur. *Perception*, *36* (ECVP Abstract).

Braddick, O., Atkinson, J., & Wattam-Bell, J. (2003). Normal and anomalous development of visual motion processing: motion coherence and 'dorsal-stream vulnerability'. *Neuropsychologia*, *41(*13), 1769-84.

Braddick, O. J., O'Brien, J. M. D., Wattam-Bell, J., Atkinson, J., & Turner, R. (2000). Form and motion coherence activate independent, but not dorsal/ventral segregated, networks in the human brain. *Current Biology*, *10*(12), 731–734.

Braddick, O. J., Wattam-Bell, J., & Atkinson, J. (1986). Orientation-specific cortical responses develop in early infancy. *Nature, 320*(6063), 617-619.

Braddick, O. J., O'Brien, J. M., Wattam-Bell, J., Atkinson, J., Hartley, T., & Turner, R. (2001). Brain areas sensitive to coherent visual motion. *Perception*, *30*(1), 61–72.

Braddick, O., Birtles, D., Mills, S., Warshafsky, J., Wattam-Bell J., & Atkinson, J. (2006). Brain responses to global perceptual coherence. Journal of Vision, 6(6), 426.

Brainard, D. H. (1997). The Psychophysics Toolbox. *Spatial Vision*, (10), 433–436.

Burton, E., Wattam-Bell, J., Rubin, G. S., Atkinson, J., Braddick, O., & Nardini, M. (2015). The effect of optical blur on cortical responses to global form and motion. *Journal of Vision, In Press*.

Campbell, F. W., & Maffei, L. (1970). Electrophysiological evidence for the existence of orientation and size detectors in the human visual system. *The Journal of Physiology*, *207*(3), 635–652.

Cavonius, C. R., & Robbins, D. O. (1973). Relationships between luminance and visual acuity in the rhesus monkey. *The Journal of Physiology*, *232*(2), 239–246.

Chaparro, A., & Young, R. S. (1989). Reading with the rod visual system. *Applied Optics*, *28*(6), 1110–1114.

Chaparro, A., & Young, R. S. (1993). Reading with rods: the superiority of central vision for rapid reading. *Investigative Ophthalmology & Visual Science*, *34*(7), 2341–2347.

Chen, J., & Sampath, A. P. (2013). Chapter 14 - Structure and Function of Rod and Cone Photoreceptors. In S. R. Schachat (Ed.), *Retina (Fifth Edition)* (pp. 342–359). London: W.B. Saunders.

Chino, Y. M., Kaas, J. H., Smith, E. d, Langston, A. L., & Cheng, H. (1992). Rapid reorganization of cortical maps in adult cats following restricted deafferentation in retina. *Vision Research*, *32*(5), 789–796.

Cleary, R., & Braddick, O. J. (1990a). Direction discrimination for band-pass filtered random dot kinematograms. *Vision Research*, *30*(2), 303–316. http://doi.org/10.1016/0042-6989(90)90045-M

Cleary, R., & Braddick, O. J. (1990b). Masking of low frequency information in short-range apparent motion. *Vision Research*, *30*(2), 317–327. http://doi.org/10.1016/0042-6989(90)90046-N

Conner, J. D. (1982). The temporal properties of rod vision. *The Journal of Physiology*, *332*(1), 139–155.

Cook, E. P., & Maunsell, J. H. (2002). Dynamics of neuronal responses in macaque MT and VIP during motion detection. *Nature Neuroscience*, *5*(10), 985–994.

Cornelissen, F., Haak, K., & Morland, A. B. (2013). Retinotopy of the cortical lesion projection zone in macular degeneration. *Perception ECVP Abstract*, *42*, 91–91.

Cutting, J. E. (1978). A program to generate synthetic walkers as dynamic point-light displays. *Behavior Research Methods*, *10*(1), 91–94.

Cynader, M., Berman, N., & Hein, A. (1973). Cats Reared in Stroboscopic Illumination: Effects on Receptive Fields in Visual Cortex. *Proceedings of the National Academy of Sciences*, *70*(5), 1353–1354.

Darian-Smith, C., & Gilbert, C. D. (1995). Topographic reorganization in the striate cortex of the adult cat and monkey is cortically mediated. *Journal of Neuroscience*, *15*(3), 1631–1647.

Daw, N. W., & Wyatt, H. J. (1976). Kittens reared in a unidirectional environment: evidence for a critical period. *The Journal of Physiology*, *257*(1), 155–170.

Ditchfield, J. A., McKendrick, A. M., & Badcock, D. R. (2006). Processing of global form and motion in migraineurs. *Vision Research*, *46*(1–2), 141–148. http://doi.org/10.1016/j.visres.2005.09.014

Duffy, C. J., & Wurtz, R. H. (1991). Sensitivity of MST neurons to optic flow stimuli. I. A continuum of response selectivity to large-field stimuli. *Journal of Neurophysiology*, *65*(6), 1329–1345.

Duffy, C. J., & Wurtz, R. H. (1995). Response of monkey MST neurons to optic flow stimuli with shifted centers of motion. *The Journal of Neuroscience*, *15*(7), 5192–5208.

Duffy, K. R., & Hubel, D. H. (2007). Receptive field properties of neurons in the primary visual cortex under photopic and scotopic lighting conditions. *Vision Research*, *47*(19), 2569–2574. http://doi.org/10.1016/j.visres.2007.06.009

Eksandh, L., Kohl, S., & Wissinger, B. (2002). Clinical features of achromatopsia in Swedish patients with defined genotypes. *Ophthalmic Genetics*, *23*(2), 109–120. http://doi.org/10.1076/opge.23.2.109.2210

Ellemberg, D., Lewis, T. L., Maurer, D., Brar, S., & Brent, H. P. (2002). Better perception of global motion after monocular than after binocular deprivation. *Vision Research*, *42*(2), 169–180.

Enoch, J. M., & Williams, R. A. (1983). Development of clinical tests of vision: Initial data on two hyperacuity paradigms. *Perception & Psychophysics*, *33*(4), 314–322. http://doi.org/10.3758/BF03205878

Essock, E. A., Williams, R. A., Enoch, J. M., & Raphael, S. (1984). The effects of image degradation by cataract on vernier acuity. *Investigative Ophthalmology & Visual Science*, *25*(9), 1043–1050.

Eysel, U. T., Schweigart, G., Mittmann, T., Eyding, D., Qu, Y., Vandesande, F., Orban, G., & Arckens, L. (1999). Reorganization in the visual cortex after retinal and cortical damage. *Restor Neurol Neurosci*, *15*(2-3), 153–164.

Felleman, D. J., & Van Essen, D. C. (1991). Distributed Hierarchical Processing in the Primate Cerebral Cortex. *Cerebral Cortex*, *1*(1), 1–47. http://doi.org/10.1093/cercor/1.1.1

Ferrera, V. P., Nealey, T. A., & Maunsell, J. H. (1994). Responses in macaque visual area V4 following inactivation of the parvocellular and magnocellular LGN pathways. *The Journal of Neuroscience*, *14*(4), 2080–2088.

Fine, I., Wade, A. R., Brewer, A. A., May, M. G., Goodman, D. F., Boynton, G. M., … MacLeod, D. I. A. (2003). Long-term deprivation affects visual perception and cortex. *Nature Neuroscience*, *6*(9), 915–916.

Freire, A., Lewis, T. L., Maurer, D., & Blake, R. (2006). The development of sensitivity to biological motion in noise. *Perception*, *35*(5), 647 – 657. http://doi.org/10.1068/p5403

Frey, R. G., Gordesch, J., Heilig, P., & Thaler, A. (1975). [Dark adaptation in achromats (mathematical analysis)(author's transl)]. *Albrecht von Graefes Archiv Fur Klinische Und Experimentelle Ophthalmologie. Albrecht von Graefe's Archive for Clinical and Experimental Ophthalmology*, *196*(3), 299–302.

Galezowski, X. (1868). *Du diagnostic des maladies des yeux par la chromatoscopie rétinienne: précédé d'une étude sur les lois physiques et physiologiques des*

couleurs, avec 31 figures, une échelle chromatique comprenant 44 teintes, et cinq échelles typographiques tirées en noir et en couleurs. Baillière.

Ganesh, S., Arora, P., Sethi, S., Gandhi, T. K., Kalia, A., Chatterjee, G., & Sinha, P. (2014). Results of late surgical intervention in children with early-onset bilateral cataracts. *British Journal of Ophthalmology*, *98*(10), 1424–1428. http://doi.org/10.1136/bjophthalmol-2013-304475

Gauthier, I., Tarr, M. J., Anderson, A. W., Skudlarski, P., & Gore, J. C. (1999). Activation of the middle fusiform'face area'increases with expertise in recognizing novel objects. *Nature Neuroscience*, *2*(6), 568–573.

Gegenfurtner, K. R., Mayser, H. M., & Sharpe, L. T. (2000). Motion perception at scotopic light levels. *JOSA A*, *17*(9), 1505–1515.

Giaschi, D. E., Regan, D., Kraft, S., & Hong, X. H. (1992). Defective processing of motion-defined form in the fellow eye of patients with unilateral amblyopia. *Investigative Ophthalmology & Visual Science*, *33*(8), 2483–2489.

Gibson, J. J. (1954). The visual perception of objective motion and subjective movement. *Psychological Review*, *61*(5), 304.

Gibson, J. J., & Gibson, E. J. (1957). Continuous perspective transformations and the perception of rigid motion. *Journal of Experimental Psychology*, *54*(2), 129.

Giese, M. A., & Poggio, T. (2003). Neural mechanisms for the recognition of biological movements. *Nature Reviews Neuroscience*, *4*(3), 179–192.

Gilaie-Dotan, S., Bentin, S., Harel, M., Rees, G., & Saygin, A. P. (2011a). Normal form from biological motion despite impaired ventral stream function. *Neuropsychologia*, *49*(5), 1033–1043. http://doi.org/10.1016/j.neuropsychologia.2011.01.009

Gilaie-Dotan, S., Bentin, S., Harel, M., Rees, G., & Saygin, A. P. (2011b). Normal form from biological motion despite impaired ventral stream function. *Neuropsychologia*, *49*(5), 1033–1043. http://doi.org/10.1016/j.neuropsychologia.2011.01.009

Gilaie-Dotan, Sharon, Kanai, R., Bahrami, B., Rees, G., & Saygin, A. P. (2013). Neuroanatomical correlates of biological motion detection. *Neuropsychologia*, *51*(3), 457–463.

Gilaie-Dotan, Sharon, Saygin, A. P., Lorenzi, L. J., Rees, G., & Behrmann, M. (2015). Ventral aspect of the visual form pathway is not critical for the perception of biological motion. *Proceedings of the National Academy of Sciences*, *112*(4), E361–E370. http://doi.org/10.1073/pnas.1414974112

Gilmore, R. O., Hou, C., Pettet, M. W., & Norcia, A. M. (2007). Development of cortical responses to optic flow. *Visual Neuroscience*, *24*(6), 845–856. http://doi.org/10.1017/S0952523807070769

Glass, L. (1969). Moire effect from random dots. *Nature*, *223*(5206), 578–580.

Glass, L., & Switkes, E. (1976). Pattern recognition in humans: Correlations which cannot be perceived. *Perception*, *5*(1), 67–72.

Glickstein, M., & Heath, G. G. (1975). Receptors in the monochromat eye. *Vision Research*, *15*(6), 633–636.

Golarai, G., Ghahremani, D. G., Whitfield-Gabrieli, S., Reiss, A., Eberhardt, J. L., Gabrieli, J. D. E., & Grill-Spector, K. (2007). Differential development of high-level visual cortex correlates with category-specific recognition memory. *Nature Neuroscience*, *10*(4), 512–522. http://doi.org/10.1038/nn1865

Goodale, M. A., & Milner, A. D. (1992). Separate visual pathways for perception and action. *Trends in Neurosciences*, *15*(1), 20–25. http://doi.org/10.1016/0166-2236(92)90344-8

Gottlob, I., & Reinecke, R. D. (1994). Eye and head movements in patients with achromatopsia. *Graefe's Archive for Clinical and Experimental Ophthalmology*, *232*(7), 392–401.

Gregory, R. L. (2003). Seeing after blindness. *Nature Neuroscience*, *6*(9), 909–910.

Grezes, J. (1998). Top down effect of strategy on the perception of human biological motion: A PET investigation. *Cognitive Neuropsychology*, *15*(6-8), 553–582.

Grill-Spector, K., Knouf, N., & Kanwisher, N. (2004). The fusiform face area subserves face perception, not generic within-category identification. *Nature Neuroscience*, *7*(5), 555–562.

Grossman, E. D., & Blake, R. (1999). Perception of coherent motion, biological motion and form-from-motion under dim-light conditions. *Vision Research*, *39*(22), 3721–3727.

Grossman, E. D., & Blake, R. (2002). Brain areas active during visual perception of biological motion. *Neuron*, *35*(6), 1167–1175.

Grossman, E., Donnelly, M., Price, R., Pickens, D., Morgan, V., Neighbor, G., & Blake, R. (2000). Brain areas involved in perception of biological motion. *Journal of Cognitive Neuroscience*, *12*(5), 711–720.

Grossman, Emily D., Battelli, L., & Pascual-Leone, A. (2005). Repetitive TMS over posterior STS disrupts perception of biological motion. *Vision Research*, *45*(22), 2847–2853.

Grossman, Emily D., & Blake, R. (2002). Brain areas active during visual perception of biological motion. *Neuron*, *35*(6), 1167–1175.

Grünert, U. (1997). Anatomical Evidence for Rod Input to the Parvocellular Pathway in the Visual System of the Primate. *European Journal of Neuroscience*, *9*(3), 617–621. http://doi.org/10.1111/j.1460-9568.1997.tb01638.x

Gunn, A., Cory, E., Atkinson, J., Braddick, O., Wattam-Bell, J., Guzzetta, A., & Cioni, G. (2002). Dorsal and ventral stream sensitivity in normal development and hemiplegia. *Neuroreport*, *13*(6), 843–847.

Hadad, B. S., Maurer, D., & Lewis, T. L. (2011). Long trajectory for the development of sensitivity to global and biological motion. *Developmental Science*, *14*(6), 1330–1339.

Hadad, B. S., Maurer, D., & Lewis, T. L. (2012). Sparing of sensitivity to biological motion but not of global motion after early visual deprivation. *Developmental Science*, *15*(4), 474-481.

Hadad, B.-S., Maurer, D., & Lewis, T. L. (2011). Long trajectory for the development of sensitivity to global and biological motion. *Developmental Science*, *14*(6), 1330–1339. http://doi.org/10.1111/j.1467-7687.2011.01078.x

Harris, L., Atkinson, J., & Braddick, O. (1976). Visual contrast sensitivity of a 6-month-old infant measured by the evoked potential. *Nature, 264(5586)*, 570-571.

Harrison, R., Hoefnagel, D., & Hayward, J. N. (1960). Congenital total color blindness: a clinicopathological report. *Archives of Ophthalmology*, *64*(5), 685.

Harvey, B. M., Braddick, O. J., & Cowey, A. (2010). Similar effects of repetitive transcranial magnetic stimulation of MT+ and a dorsomedial extrastriate site including V3A on pattern detection and position discrimination of rotating and radial motion patterns. *Journal of Vision*, *10*(5), 21. http://doi.org/10.1167/10.5.21

Hassler, P. D. R. (1966). Comparative Anatomy of the Central Visual Systems in Day- and Night-active Primates. In R. Hassler & H. Stephan (Eds.), *Evolution of the Forebrain* (pp. 419–434). Springer US.

Haxby, J. V., Gobbini, M. I., Furey, M. L., Ishai, A., Schouten, J. L., & Pietrini, P. (2001). Distributed and Overlapping Representations of Faces and Objects in Ventral Temporal Cortex. *Science*, *293*(5539), 2425–2430. http://doi.org/10.1126/science.1063736

Hayward, J., Truong, G., Partanen, M., & Giaschi, D. (2011). Effects of speed, age, and amblyopia on the perception of motion-defined form. *Vision Research*, *51*(20), 2216–2223.

Heinrich, S. P., & Bach, M. (2003). Adaptation characteristics of steady-state motion visual evoked potentials. *Clinical Neurophysiology*, *114*(7), 1359–1366.

Held, R., Ostrovsky, Y., & Sinha, P. (2008). Revisiting the molyneux question. *Journal of Vision*, *8*(6), 523–523.

Hertle, R. W., Scheiman, M. M., Beck, R. W., Chandler, D. L., Bacal, D. A., Birch, E., & Lee, K. A. (2007). Stability of visual acuity improvement following discontinuation of amblyopia treatment in children 7 to 12 years old. *Archives of Ophthalmology*, *125*(5), 655.

Hess, R. F., Mansouri, B., & Thompson, B. (2010). A new binocular approach to the treatment of Amblyopia in adults well beyond the critical period of visual development. *Restorative Neurology and Neuroscience*, *28*(6), 793–802. http://doi.org/10.3233/RNN-2010-0550

Hess, R. F., & Nordby, K. (1986a). Spatial and temporal limits of vision in the achromat. *The Journal of Physiology*, *371*(1), 365–385.

Hess, R. F., & Nordby, K. (1986b). Spatial and temporal properties of human rod vision in the achromat. *The Journal of Physiology*, *371*(1), 387–406.

Hess, R. F., Nordby, K., & Pointer, J. S. (1987). Regional variation of contrast sensitivity across the retina of the achromat: sensitivity of human rod vision. *The Journal of Physiology*, *388*(1), 101–119.

Hess, R. F., Sharpe, L. T., & Nordby, K. (1990). *Night vision: basic, clinical and applied aspects*. Cambridge University Press.

Hirai, M., Fukushima, H., & Hiraki, K. (2003). An event-related potentials study of biological motion perception in humans. *Neuroscience Letters*, *344*(1), 41–44.

Hirai, M., & Hiraki, K. (2005). An event-related potentials study of biological motion perception in human infants. *Cognitive Brain Research*, *22*(2), 301–304.

Hirai, M., Senju, A., Fukushima, H., & Hiraki, K. (2005). Active processing of biological motion perception: an ERP study. *Cognitive Brain Research*, *23*(2), 387–396.

Hirsch, H. V., & Spinelli, D. N. (1970). Visual experience modifies distribution of horizontally and vertically oriented receptive fields in cats. *Science*, *168*(3933), 869–871.

Holmes, J. M., Lazar, E. L., Melia, B. M., Astle, W. F., Dagi, L. R., Donahue, S. P., Frazier, M. G., Hertle, R. W., Repka, M. X., Quinn, G. E., Weise, K. K. (2011). Effect of age on response to amblyopia treatment in children. *Archives of Ophthalmology*, *129*(11), 1451–1457. http://doi.org/10.1001/archophthalmol.2011.179

Hood, D. C., & Finkelstein, M. A. (1986). Sensitivity to Light. In *Handbook of Perception and Human Performance, Sensory Processes and Performance* (Vol. 1). New York: John Wiley & Sons.

Hou, C., Gilmore, R. O., Pettet, M. W., & Norcia, A. M. (2009). Spatio-temporal tuning of coherent motion evoked responses in 4-6 month old infants and adults. *Vision Research*, *49*(20), 2509–2517. http://doi.org/10.1016/j.visres.2009.08.007

Hou, F., Huang, C.-B., Lesmes, L., Feng, L.-X., Tao, L., Zhou, Y.-F., & Lu, Z.-L. (2010). qCSF in Clinical Application: Efficient Characterization and Classification of Contrast Sensitivity Functions in Amblyopia. *Investigative Opthalmology & Visual Science*, *51*(10), 5365. http://doi.org/10.1167/iovs.10-5468

Hubel, D. H., & Livingstone, M. S. (1987). Segregation of form, color, and stereopsis in primate area 18. *The Journal of Neuroscience*, *7*(11), 3378–3415.

Hubel, D. H., & Wiesel, T. N. (1970). The period of susceptibility to the physiological effects of unilateral eye closure in kittens. *The Journal of Physiology*, *206*(2), 419–436.

Hubel, D. H., Wiesel, T. N., & LeVay, S. (1976). Functional architecture of area 17 in normal and monocularly deprived macaque monkeys. In *Cold Spring Harbor Symposia on Quantitative Biology* (Vol. 40, pp. 581–589). Cold Spring Harbor Laboratory Press.

Hubel, D. H., Wiesel, T. N., & LeVay, S. (1977). Plasticity of Ocular Dominance Columns in Monkey Striate Cortex. *Philosophical Transactions of the Royal Society of London B: Biological Sciences*, *278*(961), 377–409. http://doi.org/10.1098/rstb.1977.0050

Hussein, M. A. W., Coats, D. K., Muthialu, A., Cohen, E., & Paysse, E. A. (2004). Risk factors for treatment failure of anisometropic amblyopia. *Journal of American*

Association for Pediatric Ophthalmology and Strabismus, *8*(5), 429–434. http://doi.org/10.1016/j.jaapos.2003.09.005

Johansson, G. (1973). Visual perception of biological motion and a model for its analysis. *Perception & Psychophysics*, *14*(2), 201–211. http://doi.org/10.3758/BF03212378

Johnson, S., Michaelides, M., Aligianis, I. A., Ainsworth, J. R., Mollon, J. D., Maher, E. R., Moore, A. T., & Hunt, D. M. (2004). Achromatopsia caused by novel mutations in both CNGA3 and CNGB3. *Journal of Medical Genetics*, *41*(2), e20–e20.

Kaas, J. H., Krubitzer, L. A., Chino, Y. M., Langston, A. L., Polley, E. H., & Blair, N. (1990). Reorganization of retinotopic cortical maps in adult mammals after lesions of the retina. *Science*, *248*(4952), 229–31.

Kalia, A., Lesmes, L. A., Dorr, M., Gandhi, T., Chatterjee, G., Ganesh, S., Bex, P., & Sinha, P. (2014). Development of pattern vision following early and extended blindness. *Proceedings of the National Academy of Sciences of the United States of America*, *111*(5), 2035–2039. http://doi.org/10.1073/pnas.1311041111

Kanwisher, N. (2000). Domain specificity in face perception. *Nature Neuroscience*, *3*, 759–763.

Kanwisher, N., McDermott, J., & Chun, M. M. (1997). The Fusiform Face Area: A Module in Human Extrastriate Cortex Specialized for Face Perception. *The Journal of Neuroscience*, *17*(11), 4302–4311.

Kanwisher, N., & Yovel, G. (2006). The fusiform face area: a cortical region specialized for the perception of faces. *Philosophical Transactions of the Royal Society B: Biological Sciences*, *361*(1476), 2109–2128.

Kaufman, P. L., Alm, A., & Adler, F. H. (2003). *Adler's physiology of the eye: clinical application*. Mosby.

Kellnhofer, P., Ritschel, T., Vangorp, P., Myszkowski, K., & Seidel, H.-P. (2014). Stereo day-for-night: Retargeting disparity for scotopic vision. *ACM Transactions on Applied Perception (TAP)*, *11*(3), 15.

Khan, N. W., Wissinger, B., Kohl, S., & Sieving, P. A. (2007). *CNGB3* Achromatopsia with Progressive Loss of Residual Cone Function and Impaired Rod-Mediated Function. *Investigative Opthalmology & Visual Science*, *48*(8), 3864. http://doi.org/10.1167/iovs.06-1521

Kim, D., Wylie, G., Pasternak, R., Butler, P. D., & Javitt, D. C. (2006). Magnocellular contributions to impaired motion processing in schizophrenia. *Schizophrenia Research*, *82*(1), 1–8.

Kinney, J. A. S. (1958). Comparison of scotopic, mesopic, and photopic spectral sensitivity curves. *JOSA*, *48*(3), 185–190.

Kiorpes, L., Price, T., Hall-Haro, C., & Movshon, A. J. (2012). Development of sensitivity to global form and motion in macaque monkeys. *Vision Research*, *63,* 34-42.

Kobatake, E., & Tanaka, K. (1994). Neuronal selectivities to complex object features in the ventral visual pathway of the macaque cerebral cortex. *Journal of Neurophysiology*, *71*(3), 856–867.

Komáromy, A. M., Alexander, J. J., Rowlan, J. S., Garcia, M. M., Chiodo, V. A., Kaya, A., Tanaka, J. C., Acland, G. M., Hauswirth, W. W., & Aguirre, G. D. (2010). Gene therapy rescues cone function in congenital achromatopsia. *Human Molecular Genetics*, *19*(13), 2581–2593.

Kontsevich, L. L., & Tyler, C. W. (1999). Bayesian adaptive estimation of psychometric slope and threshold. *Vision Research*, *39*(16), 2729–2737.

Kosslyn, S. M., & Andersen, R. A. (1995). *Frontiers in cognitive neuroscience*. Mit Press.

Kovács, I., Kozma, P., Fehér, Á., & Benedek, G. (1999). Late maturation of visual spatial integration in humans. *Proceedings of the National Academy of Sciences*, *96*(21), 12204–12209. http://doi.org/10.1073/pnas.96.21.12204

Krakowski, A. I., Ross, L. A., Snyder, A. C., Sehatpour, P., Kelly, S. P., & Foxe, J. J. (2011). The neurophysiology of human biological motion processing: a high-density electrical mapping study. *NeuroImage*, *56*(1), 373–383.

Kravitz, D. J., Saleem, K. S., Baker, C. I., & Mishkin, M. (2011). A new neural framework for visuospatial processing. *Nature Reviews Neuroscience*, *12*(4), 217–230. http://doi.org/10.1038/nrn3008

Kravitz, D. J., Saleem, K. S., Baker, C. I., Ungerleider, L. G., & Mishkin, M. (2013). The ventral visual pathway: an expanded neural framework for the processing of object quality. *Trends in Cognitive Sciences*, *17*(1), 26–49. http://doi.org/10.1016/j.tics.2012.10.011

Lange, J. (2006). A Model of Biological Motion Perception from Configural Form Cues. *Journal of Neuroscience*, *26*(11), 2894–2906. http://doi.org/10.1523/JNEUROSCI.4915-05.2006

Lee, B. B., Smith, V. C., Pokorny, J., & Kremers, J. (1997). Rod inputs to macaque ganglion cells. *Vision Research*, *37*(20), 2813–2828.

Lee, H., Purohit, R., Sheth, V., McLean, R. J., Kohl, S., Leroy, B. P., Sundaram, V., Michaelides, M., Proudlock, F. A., & Gottlob, I. (2015). Retinal Development in Infants and Young Children with Achromatopsia. *Ophthalmology*, *122*(10), 2145-2147. http://doi.org/10.1016/j.ophtha.2015.03.033

Legge, G. E., Pelli, D. G., Rubin, G. S., & Schleske, M. M. (1985). Psychophysics of reading—I. Normal vision. *Vision Research*, *25*(2), 239–252. http://doi.org/10.1016/0042-6989(85)90117-8

Lesmes, L. A., Lu, Z.-L., Baek, J., & Albright, T. D. (2010). Bayesian adaptive estimation of the contrast sensitivity function: the quick CSF method. *Journal of Vision*, *10*(3), 17.1–21. http://doi.org/10.1167/10.3.17

Lewis, T L, Maurer, D., & Brent, H. P. (1995). Development of grating acuity in children treated for unilateral or bilateral congenital cataract. *Investigative Ophthalmology & Visual Science*, *36*(10), 2080–2095.

Lewis, T. L, Ellemberg, D., Maurer, D., Dirks, M., Wilkinson, F., & Wilson, H. R. (2004). A window on the normal development of sensitivity to global form in Glass patterns. *Perception*, *33*(4), 409–418.

Lewis, T. L., Ellemberg, D., Maurer, D., Wilkinson, F., Wilson, H. R., Dirks, M., & Brent, H. P. (2002). Sensitivity to global form in glass patterns after early visual deprivation in humans. *Vision Research*, *42*(8), 939–948.

Lewis, Terri L, Ellemberg, D., Maurer, D., Wilkinson, F., Wilson, H. R., Dirks, M., & Brent, H. P. (2002). Sensitivity to global form in glass patterns after early visual deprivation in humans. *Vision Research*, *42*(8), 939–948. http://doi.org/10.1016/S0042-6989(02)00041-X

Lewis, Terri L., Hadad, B.-S., & Maurer, D. (2010). Sensitivity to Biological and Global Motion: Similar in their Protracted Development but Different in Susceptibility to Visual Deprivation. *Journal of Vision*, *10*(7), 496–496. http://doi.org/10.1167/10.7.496

Li, J., Spiegel, D. P., Hess, R. F., Chen, Z., Chan, L. Y. L., Deng, D.,Yu, M., & Thompson, B. (2015). Dichoptic training improves contrast sensitivity in adults with amblyopia. *Vision Research*, *114*, 161–172. http://doi.org/10.1016/j.visres.2015.01.017

Liang, J., Williams, D. R., & Miller, D. T. (1997). Supernormal vision and high-resolution retinal imaging through adaptive optics. *JOSA A*, *14*(11), 2884–2892.

Livingstone, M., & Hubel, D. (1988). Segregation of form, color, movement, and depth: anatomy, physiology, and perception. *Science*, *240*(4853), 740–749.

Livingstone, M. S., & Hubel, D. H. (1994). Stereopsis and positional acuity under dark adaptation. *Vision Research*, *34*(6), 799–802.

MacLeod, D. I. (1972). Rods cancel cones in flicker. *Nature, 235*(5334)*,* 173-174.

Mandelbaum, J., & Sloan, L. L. (1947). Peripheral visual acuity: with special reference to scotopic illumination. *American Journal of Ophthalmology*, *30*(5), 581–588.

Martinez-Trujillo, J. C., Cheyne, D., Gaetz, W., Simine, E., & Tsotsos, J. K. (2007). Activation of area MT/V5 and the right inferior parietal cortex during the discrimination of

transient direction changes in translational motion. *Cerebral Cortex*, *17*(7), 1733–1739.

Mather, G., & Murdoch, L. (1994). Gender discrimination in biological motion displays based on dynamic cues. *Proceedings of the Royal Society of London. Series B: Biological Sciences*, *258*(1353), 273–279.

MATLAB. (2012). (Version 2012a). The MathWorks Inc.

Maunsell, J. H., Nealey, T. A., & DePriest, D. D. (1990). Magnocellular and parvocellular contributions to responses in the middle temporal visual area (MT) of the macaque monkey. *The Journal of Neuroscience*, *10*(10), 3323–3334.

McLeod, P., Dittrich, W., Driver, J., Perret, D., & Zihl, J. (1996). Preserved and impaired detection of structure from motion by a "motion-blind" patient. *Visual Cognition*, *3*, 363–392.

Merigan, W. H., & Maunsell, J. H. R. (1993). How Parallel are the Primate Visual Pathways? *Annual Review of Neuroscience*, *16*(1), 369–402. http://doi.org/10.1146/annurev.ne.16.030193.002101

Michaelides, M., Holder, G. E., Hunt, D. M., Fitzke, F. W., Bird, A. C., & Moore, A. T. (2005). A detailed study of the phenotype of an autosomal dominant cone-rod dystrophy (CORD7) associated with mutation in the gene for RIM1. *The British Journal of Ophthalmology*, *89*(2), 198–206. http://doi.org/10.1136/bjo.2004.050773

Michaelides, Michel. (2014). Cone and Cone–Rod Dystrophies. In *Inherited Chorioretinal Dystrophies* (pp. 151–163). Springer.

Michaelides, Michel, Hardcastle, A. J., Hunt, D. M., & Moore, A. T. (2006). Progressive Cone and Cone-Rod Dystrophies: Phenotypes and Underlying Molecular Genetic Basis. *Survey of Ophthalmology*, *51*(3), 232–258. http://doi.org/10.1016/j.survophthal.2006.02.007

Mishkin, M., & Ungerleider, L. G. (1982). Contribution of striate inputs to the visuospatial functions of parieto-preoccipital cortex in monkeys. *Behavioural Brain Research*, *6*(1), 57–77.

Mishkin, M., Ungerleider, L. G., & Macko, K. A. (1983). Object vision and spatial vision: two cortical pathways. *Trends in Neurosciences*, *6*, 414–417.

Morland, A. (2011). Organization of primary visual maps in patients with retinal lesions. *Journal of Vision*, *11*(15), 73–73.

Morrone, M. C., Tosetti, M., Montanaro, D., Fiorentini, A., Cioni, G., & Burr, D. C. (2000). A cortical area that responds specifically to optic flow, revealed by fMRI. *Nature Neuroscience*, *3*(12), 1322–1328.

Morrone, M. Concetta, Burr, D. C., & Fiorentini, A. (1993). Development of infant contrast sensitivity to chromatic stimuli. *Vision Research*, *33*(17), 2535–2552.

Movshon, J. A., & Blakemore, C. (1974). Functional reinnervation in kitten visual cortex. *Nature*, *251*(5475), 504-505.

Neri, P., Luu, J. Y., & Levi, D. M. (2007). Sensitivity to biological motion drops by 1/2 log-unit with inversion, and is unaffected by amblyopia. *Vision Research*, *47*(9), 1209–1214.

Neri, P., Morrone, M. C., & Burr, D. C. (1998). Seeing biological motion. *Nature*, *395*(6705), 894–896.

Newsome, W. T., & Pare, E. B. (1988). A selective impairment of motion perception following lesions of the middle temporal visual area (MT). *The Journal of Neuroscience*, *8*(6), 2201–2211.

Nishiguchi, K. M., Sandberg, M. A., Gorji, N., Berson, E. L., & Dryja, T. P. (2005). Cone cGMP-gated channel mutations and clinical findings in patients with achromatopsia, macular degeneration, and other hereditary cone diseases. *Human Mutation*, *25*(3), 248–258. http://doi.org/10.1002/humu.20142

Norcia, A. M., Pei, F., Bonneh, Y., Hou, C., Sampath, V., & Pettet, M. W. (2005). Development of sensitivity to texture and contour information in the human infant.

Journal of Cognitive Neuroscience, *17*(4), 569–579. http://doi.org/10.1162/0898929053467596

Nygaard, R. W., & Frumkes, T. E. (1985). Frequency dependence in scotopic flicker sensitivity. *Vision Research*, *25*(1), 115–127.

Odom, J. V., Bach, M., Brigell, M., Holder, G. E., McCulloch, D. L., & Tormene, A. P. (2010). ISCEV standard for clinical visual evoked potentials (2009 update). *Documenta Ophthalmologica*, *120*(1), 111–119.

Olejniczak, P. (2006). Neurophysiologic Basis of EEG: *Journal of Clinical Neurophysiology*, *23*(3), 186–189. http://doi.org/10.1097/01.wnp.0000220079.61973.6c

Oliver, M., Neumann, R., Chaimovitch, Y., Gotesman, N., & Shimshoni, M. (1986). Compliance and results of treatment for amblyopia in children more than 8 years old. *American Journal of Ophthalmology*, *102*(3), 340.

Oram, M. W., & Perrett, D. I. (1994). Responses of anterior superior temporal polysensory (STPa) neurons to "biological motion" stimuli. *Journal of Cognitive Neuroscience*, *6*(2), 99–116.

Orban, G., Kennedy, H., Maes, H., & Amblard, B. (1978). Cats reared in stroboscopic illumination: Velocity characteristics of Area 18 neurons. *Archives Italiennes de Biologie*, *116*(3-4), 413–419.

Orban, G. A., Lagae, L., Verri, A., Raiguel, S., Xiao, D., Maes, H., & Torre, V. (1992). First-order analysis of optical flow in monkey brain. *Proceedings of the National Academy of Sciences*, *89*(7), 2595–2599.

Ostrovsky, Y., Andalman, A., & Sinha, P. (2006). Vision following extended congenital blindness. *Psychological Science*, *17*(12), 1009–1014.

Ostwald, D., Lam, J. M., Li, S., & Kourtzi, Z. (2008). Neural Coding of Global Form in the Human Visual Cortex. *Journal of Neurophysiology*, *99*(5), 2456–2469. http://doi.org/10.1152/jn.01307.2007

Palomares, M., Pettet, M., Vildavski, V., Hou, C., & Norcia, A. (2009). Connecting the Dots: How Local Structure Affects Global Integration in Infants. *Journal of Cognitive Neuroscience*, *22*(7), 1557–1569. http://doi.org/10.1162/jocn.2009.21323

Pasternak, T., Merigan, W. H., & Movshon, J. A. (1981). Motion mechanisms in strobe-reared cats: Psychophysical and electrophysical measures. *Acta Psychologica*, *48*(1–3), 321–332. http://doi.org/10.1016/0001-6918(81)90071-8

Pastor, M. A., Artieda, J., Arbizu, J., Valencia, M., & Masdeu, J. C. (2003). Human cerebral activation during steady-state visual-evoked responses. *The Journal of Neuroscience*, *23*(37), 11621–11627.

PASW STATISTICS. (2009). (Version 18.0). Chicago, IL: IBM.

Paviova, M., Krägeloh-Mann, I., Sokolov, A., & Birbaumer, N. (2001). Recognition of point-light biological motion displays by young children. *Perception*, *30*(8), 925–933.

Pavlova, M., Krägeloh-Mann, I., Sokolov, A., & Birbaumer, N. (2001). Recognition of point-light biological motion displays by young children. *Perception*, *30*(8), 925–933.

Peelen, M. V., Wiggett, A. J., & Downing, P. E. (2006). Patterns of fMRI Activity Dissociate Overlapping Functional Brain Areas that Respond to Biological Motion. *Neuron*, *49*(6), 815–822. http://doi.org/10.1016/j.neuron.2006.02.004

Pelli, D. G., Robson, J. G., & Wilkinson, A. J. (1988). The design of a new letter chart for measuring contrast sensitivity. In *Clinical Vision Sciences*, *2*(3), 187-199.

Picton, T. W., Bentin, S., Berg, P., Donchin, E., Hillyard, S. A., Johnson Jr, R., Miller, G. A., Ritter, W., Ruchkin, D. S., Rugg, M. D. & Taylor, M. J. (2000). Guidelines for using human event-related potentials to study cognition: Recording standards and publication criteria. *Psychophysiology*, *37*(2), 127–152.

Pinto, J., & Shiffrar, M. (1999). Subconfigurations of the human form in the perception of biological motion displays. *Acta Psychologica*, *102*(2–3), 293–318. http://doi.org/10.1016/S0001-6918(99)00028-1

Prazdny, K. (1984). On the perception of Glass patterns. *Perception*, *13*(4), 469–478.

Prins, N. (2012). The psychometric function: The lapse rate revisited. *Journal of Vision*, *12*(6), 25–25. http://doi.org/10.1167/12.6.25

Puce, A., & Perrett, D. (2003a). Electrophysiology and brain imaging of biological motion. *Philosophical Transactions of the Royal Society of London. Series B: Biological Sciences*, *358*(1431), 435–445.

Puce, A., & Perrett, D. (2003b). Electrophysiology and brain imaging of biological motion. *Philosophical Transactions of the Royal Society of London. Series B: Biological Sciences*, *358*(1431), 435–445.

Purves, D., Augustine, G. J., Fitzpatrick, D., Katz, L. C., LaMantia, A.-S., McNamara, J. O., & Williams, S. M. (2001). Anatomical Distribution of Rods and Cones. In *Neuroscience (2nd Edition)*. Sunderland, MA: Sinauer Associates.

Reid, V. M., Hoehl, S., & Striano, T. (2006). The perception of biological motion by infants: An event-related potential study. *Neuroscience Letters*, *395*(3), 211–214.

Remmer, M. H., Rastogi, N., Ranka, M. P., & Ceisler, E. J. (2015). Achromatopsia: a review. [Miscellaneous Article]. *Current Opinion in Ophthalmology*, *26*(5), 333–340. http://doi.org/10.1097/ICU.0000000000000189

RetNet, http://www.sph.uth.tmc.edu/RetNet/.

Riesenhuber, M., & Poggio, T. (1999). Hierarchical models of object recognition in cortex. *Nature Neuroscience*, *2*(11), 1019–1025.

Riggs, L. A. (1965). Visual Acuity. In *Vision and Visual Perception* (p. 324). New York: Wiley.

Rizzolatti, G., & Craighero, L. (2004). The mirror-neuron system. *Annu. Rev. Neurosci.*, *27*, 169–192.

Rizzolatti, G., Fadiga, L., Fogassi, L., & Gallese, V. (1999). Resonance behaviors and mirror neurons. *Archives Italiennes de Biologie*, *137*(2), 85–100.

Rosenberg, T., Baumann, B., Kohl, S., Zrenner, E., Jorgensen, A. L., & Wissinger, B. (2004). Variant Phenotypes of Incomplete Achromatopsia in Two Cousins with *GNAT2* Gene

Mutations. *Investigative Opthalmology & Visual Science*, *45*(12), 4256. http://doi.org/10.1167/iovs.04-0317

Sacks, O. (1996). *The island of the colour-blind: and, Cycad Island*. Pan Macmillan.

Saxe, R., Xiao, D.-K., Kovacs, G., Perrett, D. I., & Kanwisher, N. (2004). A region of right posterior superior temporal sulcus responds to observed intentional actions. *Neuropsychologia*, *42*(11), 1435–1446.

Saygin, A. P. (2007). Superior temporal and premotor brain areas necessary for biological motion perception. *Brain*, *130*(9), 2452–2461.

Saygin, Ayse Pinar, Wilson, S. M., Hagler Jr, D. J., Bates, E., & Sereno, M. I. (2004). Point-light biological motion perception activates human premotor cortex. *The Journal of Neuroscience*, *24*(27), 6181–6188.

Schmid, L. M., Rosa, M. G., & Calford, M. B. (1995). Retinal detachment induces massive immediate reorganization in visual cortex. *Neuroreport*, *6*(9), 1349–1353.

Simion, F., Regolin, L., & Bulf, H. (2008). A predisposition for biological motion in the newborn baby. *Proceedings of the National Academy of Sciences*, *105*(2), 809–813.

Simunovic, M. P., Regan, B. C., & Mollon, J. D. (2001). Is color vision deficiency an advantage under scotopic conditions? *Investigative Ophthalmology and Visual Science*, *42*(13), 3357–3364.

Sincich, L. C., & Horton, J. C. (2005). The circuitry of V1 and V2: integration of color, form, and motion. *Annu. Rev. Neurosci.*, *28*, 303–326.

Sloan, L. L. (1954). Congenital achromatopsia: a report of 19 cases. *JOSA*, *44*(2), 117–128.

Sloan, L. L., & Feiock, K. (1972). Acuity-luminance function in achromatopsia and in progressive cone degeneration: factors related to individual differences in tolerance to bright light. *Investigative Ophthalmology & Visual Science*, *11*(10), 862–868.

Smirnakis, S. M., Brewer, A. A., Schmid, M. C., Tolias, A. S., Schüz, A., Augath, M., Inhoffen, W., Wanell, B. A., & Logothetis, N. K. (2005). Lack of long-term cortical reorganization after macaque retinal lesions. *Nature*, *435*(7040), 300–307.

Smith, A. T., Snowden, R. J., & Milne, A. B. (1994). Is global motion really based on spatial integration of local motion signals? *Vision Research*, *34*(18), 2425–2430.

Smith, M. A., Bair, W., & Movshon, J. A. (2002). Signals in macaque striate cortical neurons that support the perception of glass patterns. *The Journal of Neuroscience*, *22*(18), 8334–8345.

Snowden, R. J., & Braddick, O. J. (1989). The combination of motion signals over time. *Vision Research*, *29*(11), 1621–1630.

Spencer, J., O'Brien, J., Riggs, K., Braddick, O., Atkinson, J., & Wattam-Bell, J. (2000). Motion processing in autism: evidence for a dorsal stream deficiency. *Neuroreport*, *11*(12), 2765–2767.

Spencer, Janine, O'Brien, J., Riggs, K., Braddick, O., Atkinson, J., & Wattam-Bell, J. (2000). Motion processing in autism: evidence for a dorsal stream deficiency. *Neuroreport*, *11*(12), 2765–2767.

Stockman, A., & Sharpe, L. T. (2006). Into the twilight zone: the complexities of mesopic vision and luminous efficiency. *Ophthalmic and Physiological Optics*, *26*(3), 225–239. http://doi.org/10.1111/j.1475-1313.2006.00325.x

Sun, H., Pokorny, J., & Smith, V. C. (2001). Rod-cone interactions assessed in inferred magnocellular and parvocellular postreceptoral pathways. *Journal of Vision*, *1*(1), 5.

Sundaram, V., Wilde, C., Aboshiha, J., Cowing, J., Han, C., Langlo, C. S., Chana, R., Davidson, A.E., Sergouniotis, P. I., Bainbridge, J. W., Ali, R. R., Dubra, A., Rubin, G., Webster, A. R., Moore, A. T., Nardini, M., Carroll, J., & Michaelides, M. (2014). Retinal structure and function in achromatopsia: implications for gene therapy. *Ophthalmology*, *121*(1), 234–245.

Sundin, O. H., Yang, J. M., Li, Y., Zhu, D., Hurd, J. N., Mitchell, T. N., Silva, E. D., & Maumenee, I. H. (2000). Genetic basis of total colourblindness among the Pingelapese islanders. *Nature Genetics*, *25*(3), 289–293. http://doi.org/10.1038/77162

Sweeny, T. D., Wurnitsch, N., Gopnik, A., & Whitney, D. (2013). Sensitive perception of a person's direction of walking by 4-year-old children. *Developmental Psychology*, *49*(11), 2120–2124. http://doi.org/10.1037/a0031714

Takeuchi, T., & De Valois, K. K. (2000). Velocity discrimination in scotopic vision. *Vision Research*, *40*(15), 2011–2024.

Taylor, N. M., Jakobson, L. S., Maurer, D., & Lewis, T. L. (2009). Differential vulnerability of global motion, global form, and biological motion processing in full-term and preterm children. *Neuropsychologia*, *47*(13), 2766–2778.

Teller, D. Y. (2009). Scotopic vision, color vision, and stereopsis in infants. *Current Eye Research, 2*(3), 199-210.

Thiadens, A. A., Somervuo, V., van den Born, L. I., Roosing, S., van Schooneveld, M. J., Kuijpers, R. W., van Moll-Ramirez, N., Cremers, F. P., Hoyng, C. B., & Klaver, C. C. W. (2010). Progressive loss of cones in achromatopsia: an imaging study using spectral-domain optical coherence tomography. *Investigative Ophthalmology & Visual Science*, *51*(11), 5952–5957.

Thiadens, Alberta A.H.J., Phan, T. M. L., Zekveld-Vroon, R. C., Leroy, B. P., van den Born, L. I., Hoyng, C. B., Klaver, C. C., Roosing, S., Pott, J. W., van Schooneveld, M. K., van Moll-Ramirez, N., van Genderen, M. M., Boon, C. J., den Hollander, A. I., Bergen, A. A., De Baere, A. A., Cremers, F. P., & Lotery, A. J. (2012). Clinical Course, Genetic Etiology, and Visual Outcome in Cone and Cone–Rod Dystrophy. *Ophthalmology*, *119*(4), 819–826. http://doi.org/10.1016/j.ophtha.2011.10.011

Thompson, B., Villeneuve, M. Y., Casanova, C., & Hess, R. F. (2012). Abnormal cortical processing of pattern motion in amblyopia: evidence from fMRI. *NeuroImage*, *60*(2), 1307–1315. http://doi.org/10.1016/j.neuroimage.2012.01.078

Thompson, Benjamin, Aaen-Stockdale, C. R., Mansouri, B., & Hess, R. F. (2008). Plaid perception is only subtly impaired in strabismic amblyopia. *Vision Research*, *48*(11), 1307–1314. http://doi.org/10.1016/j.visres.2008.02.020

Thompson, Benjamin, Troje, N. F., Hansen, B. C., & Hess, R. F. (2008). Amblyopic perception of biological motion. *Journal of Vision*, *8*(4), 22.

Tong, F., Nakayama, K., Moscovitch, M., Weinrib, O., & Kanwisher, N. (2000). Response properties of the human fusiform face area. *Cognitive Neuropsychology*, *17*(1-3), 257–280.

Vaina, L. M., Solomon, J., Chowdhury, S., Sinha, P., & Belliveau, J. W. (2001). Functional neuroanatomy of biological motion perception in humans. *Proceedings of the National Academy of Sciences*, *98*(20), 11656–11661.

Vaina, Lucia M., Lemay, M., Bienfang, D. C., Choi, A. Y., & Nakayama, K. (1990). Intact "biological motion" and "structure from motion" perception in a patient with impaired motion mechanisms: A case study. *Visual Neuroscience*, *5*(04), 353–369. http://doi.org/10.1017/S0952523800000444

Van Nes, F. L., Koenderink, J. J., Nas, H., & Bouman, M. A. (1967). Spatiotemporal modulation transfer in the human eye. *Journal of the Optical Society of America*, *57*(9), 1082–1088.

Vanrie, J., & Verfaillie, K. (2004). Perception of biological motion: A stimulus set of human point-light actions. *Behavior Research Methods*, *36*(4), 625–629.

Victor, J. D., Conte, M. M., Burton, L., & Nass, R. D. (1993). Visual evoked potentials in dyslexics and normals: failure to find a difference in transient or steady-state responses. *Visual Neuroscience*, *10*, 939–939.

Victor, J. D., & Mast, J. (1991). A new statistic for steady-state evoked potentials. *Electroencephalography and Clinical Neurophysiology*, *78*(5), 378–388.

Vedamurthy, I., Nahum, M., Huang, S. J., Zheng, F., Bayliss, J., Bavelier, D., & Levi, D. M. (2015). A dichoptic custom-made action video game as a treatment for adult amblyopia. *Vision Research*, *114*, 173–187. http://doi.org/10.1016/j.visres.2015.04.008

Watamaniuk, S. N., McKee, S. P., & Grzywacz, N. M. (1995). Detecting a trajectory embedded in random-direction motion noise. *Vision Research*, *35*(1), 65–77.

Watson, J. D., Myers, R., Frackowiak, R. S., Hajnal, J. V., Woods, R. P., Mazziotta, J. C., … Zeki, S. (1993). Area V5 of the human brain: evidence from a combined study using positron emission tomography and magnetic resonance imaging. *Cerebral Cortex*, *3*(2), 79–94.

Wattam-Bell, J. (1996). Visual motion processing in one-month-old infants: habituation experiments. *Vision Research*, *36*(11), 1679–1685.

Wattam-Bell, J., Birtles, D., Nyström, P., von Hofsten, C., Rosander, K., Anker, S., Atkinson, J., & Braddick, O. (2010). Reorganization of global form and motion processing during human visual development. *Current Biology*, *20*(5), 411–415.

Wattam-Bell, J., Corbett, F., & Chelliah, V. (2013). Coherence sensitivity of cortical responses to global form. *Perception ECVP Abstract*, *42*, 55–55.

Wattam-Bell, J. (1991). Development of motion-specific cortical responses in infancy. *Vision Research*, *31*(2), 287–297.

Weinstein, J. M., Gilmore, R. O., Shaikh, S. M., Kunselman, A. R., Trescher, W. V., Tashima, L. M., Boltz, M. E., McAuliffe, M. B., Cheung, A., & Fesi, J. D. (2012). Defective motion processing in children with cerebral visual impairment due to periventricular white matter damage. *Developmental Medicine & Child Neurology*, *54*(7), e1–e8.

Westheimer, G. (1965). Spatial interaction in the human retina during scotopic vision. *The Journal of Physiology*, *181*(4), 881–894.

Westheimer, G., & McKee, S. P. (1980). Stereoscopic acuity with defocused and spatially filtered retinal images. *Journal of the Optical Society of America*, *70*(7), 772–778. http://doi.org/10.1364/JOSA.70.000772

Wick, B., Wingard, M., Cotter, S., & Scheiman, M. (1992). Anisometropic amblyopia: is the patient ever too old to treat? *Optometry and Vision Science: Official Publication of the American Academy of Optometry*, *69*(11), 866–878.

Wickens, A. (2009). *Introduction to Biopsychology*. Pearson Education.

Wiesel, T. N., & Hubel, D. H. (1974). Ordered arrangement of orientation columns in monkeys lacking visual experience. *Journal of Comparative Neurology*, *158*(3), 307–318.

Wilkinson, F., James, T. W., Wilson, H. R., Gati, J. S., Menon, R. S., & Goodale, M. A. (2000). An fMRI study of the selective activation of human extrastriate form vision areas by radial and concentric gratings. *Current Biology*, *10*(22), 1455–1458. http://doi.org/10.1016/S0960-9822(00)00800-9

Williams, R. A., Enoch, J. M., & Essock, E. A. (1984). The resistance of selected hyperacuity configurations to retinal image degradation. *Investigative Ophthalmology & Visual Science*, *25*(4), 389–399.

Wilson, H. R., & Wilkinson, F. (1998). Detection of global structure in Glass patterns: implications for form vision. *Vision Research*, *38*(19), 2933–2947.

Wilson, H. R., Wilkinson, F., & Asaad, W. (1997). Concentric orientation summation in human form vision. *Vision Research*, *37*(17), 2325–2330.

Wissinger, B., Gamer, D., Jägle, H., Giorda, R., Marx, T., Mayer, S., Tippmann, S., Broghammer, M., Jurklies, B., Rosenberg, T., Jacobson, S. G., Cumhur Sener, E., Tatlipinar, S., Hoyng, C. B., Castellan, C., Bitoun, P., Andreasson, S., Gunter, R., Kellner, U., Lorenz, B., Wolff, G., Verellen,-Doumoulin, C., Schwartz, M., Cremers, F. P. M., Apfelstedt-Sylla, E., Zrenner, E., Salati, R., Sharpe, L. T., & Kohl, S. (2001). CNGA3 Mutations in Hereditary Cone Photoreceptor Disorders. *American Journal of Human Genetics*, *69*(4), 722–737.

Wu, H., Cowing, J. A., Michaelides, M., Wilkie, S. E., Jeffery, G., Jenkins, S. A., Mester, V., Bird, A. C., Robson, A. G., Holder, G. E., Moore, A. T., Hunt, D. M., & Webster, A. R.

(2006). Mutations in the Gene KCNV2 Encoding a Voltage-Gated Potassium Channel Subunit Cause “Cone Dystrophy with Supernormal Rod Electroretinogram” in Humans. *American Journal of Human Genetics*, *79*(3), 574–579.

Xu, Y. (2005). Revisiting the role of the fusiform face area in visual expertise. *Cerebral Cortex*, *15*(8), 1234–1242.

Yang, P., Michaels, K. V., Courtney, R. J., Wen, Y., Greninger, D. A., Reznick, L., Karr, D. J., Wilson, L. B., Weleber, R. G., & Pennesi, M. E. (2014). Retinal morphology of patients with achromatopsia during early childhood: implications for gene therapy. *JAMA Ophthalmology*, *132*(7), 823–831.

Ye, G., Budzynski, E., Sonnentag, P., Nork, M., Sheibani, N., Boye, S. L., Hauswirth, W. W., & Chulay, J. D. (2014). Development and Evaluation of Cone-Specific Promoters in Non-human Primates for Gene Therapy of Congenital Cone Diseases Including Achromatopsia. *Investigative Ophthalmology & Visual Science*, *55*(13), 837–837.

Zhao, J., Wang, L., Wang, Y., Weng, X., Li, S., & Jiang, Y. (2014). Developmental tuning of reflexive attentional effect to biological motion cues. *Scientific Reports*, *4*(5558), 1-5. http://doi.org/10.1038/srep05558

Zwicker, A. E., Hoag, R. A., Edwards, V. T., Boden, C., & Giaschi, D. E. (2006). The Effects of Optical Blur on Motion and Texture Perception. *Optometry and Vision Science*, *83*(6), 382–390. http://doi.org/10.1097/01.opx.0000222919.21909.1e

LIST OF APPENDICES

APPENDIX I – ETHICS DOCUMENTS

- Consent forms
    - Controls
    - Stationary cone dystrophy
    - Progressive cone dystrophy

- Control information sheet
    - Blur Study
    - Low light study

- Patient information sheet

- Subject expenses form

Informed Consent Form for Participants in Research Studies

Please complete this form after you have read the Information Sheet and/or listened to an explanation about the research.

Title of Project: **Form and motion under [blur/ low light]**

This study has been approved by the UCL Research Ethics Committee [Project ID Number: CPB_2014_007]

Thank you for your interest in taking part in this research. Before you agree to take part the person organising the research must explain the project to you.

If you have any questions arising from the Information Sheet or explanation already given to you, please ask the researcher before you to decide whether to join in. You will be given a copy of the Information Sheet to keep and refer to at any time.

Participant's Statement

I …….

- have read the notes written above and the Information Sheet, and understand what the study involves.
- understand that if I decide at any time that I no longer wish to take part in this project, I can notify the researchers involved and withdraw immediately.
- consent to the processing of my personal information for the purposes of this research study.
- understand that such information will be treated as strictly confidential and handled in accordance with the provisions of the Data Protection Act 1998.
- agree that my non-personal research data may be used by others for future research. I am assured that the confidentiality of my personal data will be upheld through the removal of identifiers.
- agree that the research project named above has been explained to me to my satisfaction and I agree to take part in this study.

Participant's name:

Date:

Signed:

CONSENT FORM

Title of Project: A study of form and motion processing in achromatopsia

Researchers: Ms Eliza Burton, Dr Marko Nardini, Dr John Wattam-Bell

Please initial box

1. I confirm that I have read and understand the information sheet dated 28.03.2012 (Version 1.0) for the above study and have had the opportunity to ask questions. ☐

2. I understand that my participation is voluntary and that I am free to withdraw at any time, without giving any reason and without my medical care or legal rights being affected. ☐

3. I agree to the researchers on this project having access to my medical notes for the purpose of obtaining details relevant to the study. ☐

4. I agree that my GP can be informed about my participation in this study. ☐

5. I agree to take part in the above study. ☐

_____	_____	_____
Name of Participant	Date	Signature

_____	_____	_____
Name of Researcher	Date	Signature

CONSENT FORM

Title of Project: A study of form and motion processing in cone dystrophy patients

Researchers: Ms Eliza Burton, Dr Marko Nardini, Dr John Wattam-Bell

Please initial box

1. I confirm that I have read and understand the information sheet dated 14.09.2012 (Version 1.0) for the above study and have had the opportunity to ask questions. ☐

2. I understand that my participation is voluntary and that I am free to withdraw at any time, without giving any reason, without my medical care or legal rights being affected. ☐

3. I agree to the researchers on this project having access to my medical notes for the purpose of obtaining details relevant to the study. ☐

4. I agree that my GP can be informed about my participation in this study. ☐

5. I agree to take part in the above ☐

study.

_____	_____	_____
Name of Participant	Date	Signature

_____	_____	_____
Name of Participant	Date	Signature

Form and Motion Under Blur

Information Sheet

We would like to invite you to participate in this research project.

You should only participate if you want to; choosing not to take part will not disadvantage you in any way. Before you decide whether you want to take part, it is important to read the following information carefully and discuss it with others if you wish. Ask if there is anything that is not clear or if you would like more information.

The aim of the study is to assess the impact of reduced vision on form and motion processing. This will inform us of how form and motion processing can be affected when a person has a visual impairment.

For the study we will first ask you to complete an eye test, reading letters on a screen. This will be done under different degrees of blurriness created using blurring lenses and filters placed over the screen.

Once your vision under blur has been assessed we will begin the main experiment, consisting of two parts. Part one involves a number of computer based tests in which you will be asked to identify visual patterns on a screen under varying amounts of blur. The blur will be achieved by placing a filter over the computer monitor. Part two involves an EEG which allows us to record your brain activation in real time as you view patterns on a monitor.

For the EEG we will ask you to wear an EEG cap. This consists of a number of small tubes attached to sponges which rest on your head and record electrical activity along the scalp. EEG is a non-invasive and safe technique which records your naturally occurring brain waves (so no electrical current will be applied to your head). While the procedure is reasonably comfortable, the cap is soaked in water, salt and shampoo before being placed on your head (to increase the conductivity), so your hair will get slightly wet during the experiment.

The study takes 2.5 hours in total. It is up to you to decide whether or not to take part. If you decide to take part you will be given this information sheet to keep and will be asked to sign a consent form. If you decide to take part you are still free to withdraw at any time and without giving a reason.

Thank you for taking the time to read this information sheet.

All data will be collected and stored in accordance with the Data Protection Act 1998. We will keep data from the study in an anonymised form.

Dark Adapted Form and Motion

Information Sheet

We would like to invite you to participate in this research project.

You should only participate if you want to; choosing not to take part will not disadvantage you in any way. Before you decide whether you want to take part, it is important to read the following information carefully and discuss it with others if you wish. Ask if there is anything that is not clear or if you would like more information.

The aim of the study is to assess the impact low light may have on the detection of form and motion. This information will then be used to develop new vision tests for patients with Achromatopsia – a condition in which people have no colour vision and can see best in dim light.

You will complete the study in 4 light conditions. In order for your eyes to be completely adapted to the dark you will need to sit in dark room for 30 minutes before we proceed with the tests. Part 1 of the experiment will involve a series of computer tasks. Part 2 will involve an EEG which allows us to record your brain activation in real time as you view patterns on a monitor.

For the computer tasks in each light condition you will be presented with a screen containing an object (a shape or movement) on one half and random dots or lines on the other. We would like you to respond using a keyboard to which half of the screen you see the stimulus on. You will be tested on four types of stimuli – form, motion, biological motion and gratings (striped patterns). Examples of these will be shown to you before you start so you know what you are looking for.

For the EEG we will ask you to wear an EEG cap. This consists of a number of small tubes attached to sponges which rest on your head and record electrical activity along the scalp. EEG is a non-invasive and safe technique which records your naturally occurring brain waves (so no electrical current will be applied to your head). While the procedure is reasonably comfortable, the cap is soaked in water, salt and shampoo before being placed on your head (to increase the conductivity), so your hair will get slightly wet during the experiment.

The study will last up to 4 hours in total. You will receive £30 for your time.

It is up to you to decide whether or not to take part. If you decide to take part you will be given this information sheet to keep and will be asked to sign a consent form. If you decide to take part you are still free to withdraw at any time and without giving a reason.

Thank you for taking the time to read this information sheet.

All data will be collected and stored in accordance with the Data Protection Act 1998. We will keep data from the study in an anonymised form.

Adult Patient Information Sheet

A study of form and motion processing in achromatopsia

PLEASE CONTACT US IF YOU WOULD LIKE THIS LEAFLET IN LARGER TYPE OR THE INFORMATION PROVIDED ON CD

You are being invited to take part in this research study. Before you decide, it is important for you to understand why the research is being done and what it will involve. Please take time to read the following information carefully and discuss it with friends, relatives and your GP if you wish. If you need more information please contact the research team whose telephone number is at the end of this leaflet.

What is the purpose of the study?

This research study aims to provide detailed information about how the brain processes visual information in patients with achromatopsia. We are measuring how people with achromatopsia perceive visual shapes (form) and visual motion, and how form and motion perception is carried out by different visual areas in the brain. We hope that this will lead to a better understanding of the condition, assist in providing improved information to patients and also assist in developing future treatment strategies.

Do I have to take part?

It is up to you to decide whether or not to take part. If you decide to take part you are still free to withdraw at any time and without giving a reason. A decision to withdraw at any time, or a decision not to take part, will not affect the standard of care you receive.

What will happen to me if I take part?

You will be asked to take part in a series of tests looking at your vision under different light levels. The tests will take place across two half day sessions. These may be on a single day, taking place in the morning and afternoon, or on two separate days.

The first session will involve a series of computer based tests, while the second session will involve electroencephalogram (EEG) measures. EEG is a safe and non-invasive technique that allows us to measure brain activity by placing small sensors on the scalp.

For the computer based tests you will see patterns on a computer screen which may be moving or stationary. You will need to make judgements about the patterns, for example you may have to determine the direction of the movement on the screen, or you may have to indicate on which side of the screen you can see a shape. These tests will be carried out under a number of different light levels so that we can see how this affects your vision. When you do the tests under the lowest light levels we will first ask you to sit wearing dark goggles for 30 minutes to allow your eyes to adapt to the dark. During this time you can listen to music or a radio show. We will also ask you to wear dark glasses, similar to sun glasses, for some of the tests, to make it extra dark.

For the second session, we will place an EEG cap on your head. This is similar to a swimming cap but contains many small sensors that rest on the head and are able to pick up changes in brain activity. The cap is soaked in a salt solution to increase its conductivity so you may get a slightly wet scalp during the tests. This usually dries out over the course of the session but we will provide you with towels and a hairdryer if needed. Whilst wearing the EEG cap we will ask you to observe patterns on a computer screen, similar to those seen in the first session. While you view these we will record your brain activity.

The tests will take place at University College London, approximately 2 miles west of Moorfields Eye Hospital.

We will usually refund travel expenses which can be towards public transport costs or petrol money (45p/mile) and parking.

What are the possible disadvantages or risks of taking part?

There are no known disadvantages or risks.

What are the possible benefits of taking part?

These investigations will provide detailed information regarding the functioning of the visual brain in achromatopsia. The findings of this study will help gain a more accurate understanding of achromatopsia and we hope that it will also be valuable in helping to develop future treatments.

What if something goes wrong?

The research does not carry any more risks than a normal visit to the hospital, or completing a routine vision test. If taking part in this research project harms you, there are no special compensation arrangements. If you are harmed due to someone's negligence, then you may have grounds for a legal action but you may have to pay for it. Regardless of this, if you wish to complain about any aspect of the way you have been approached or treated during the course of this study, the normal National Health Service complaints mechanisms will be available to you.

Will my information be kept confidential?

All information collected for the study will be kept strictly confidential. The research team will not pass on your personal details to anyone else.

What will happen to the results of the research study?

All the information from the study will be published in medical journals and presented to relevant health professionals at meetings and conferences. We would also be pleased to provide information about the results of the study to anyone who has taken part. Individual patients will not be identified in any reports or publications arising from the study.

Contacts for further information

For specific questions about the research, please contact either:

Investigator:

Ms Eliza Burton

UCL Institute of Ophthalmology

Phone: 0207 608 6819

Email: eliza.burton@ucl.ac.uk

Chief Investigator:

Dr Marko Nardini

UCL Institute of Ophthalmology

Phone: 0207 608 6909

email: m.nardini@ucl.ac.uk

Thank you for reading this and considering taking part in this study

Adult Patient Information Sheet

A study of form and motion processing in cone dystrophy patients

PLEASE CONTACT US IF YOU WOULD LIKE THIS LEAFLET IN LARGER TYPE

You are being invited to take part in this research study. Before you decide, it is important for you to understand why the research is being done and what it will involve. Please take time to read the following information carefully and discuss it with friends, relatives and your GP if you wish. If you need more information please contact the research team whose telephone number is at the end of this leaflet.

What is the purpose of the study?

This research study aims to provide detailed information about how the brain processes visual information in patients with cone dystrophies. We are measuring how people perceive visual shapes (form) and visual motion, and how form and motion perception is carried out by different visual areas in the brain. We hope that this will lead to a better understanding of form and motion perception, assist in providing improved information to patients and also assist in developing future treatment strategies.

Do I have to take part?

It is up to you to decide whether or not to take part. If you decide to take part you are still free to withdraw at any time and without giving a reason. A decision to withdraw at any time, or a decision not to take part, will not affect the standard of care you receive.

What will happen to me if I take part?

You will be asked to take part in a series of tests looking at your vision under different light levels. The tests will take place across two half day sessions. These may be on a single day, taking place in the morning and afternoon, or on two separate days.

The first session will involve a series of computer based tests, while the second session will involve electroencephalogram (EEG) measures. EEG is a safe and non-invasive technique that allows us to measure brain activity by placing small sensors on the scalp.

For the computer based tests you will see patterns on a computer screen which may be moving or stationary. You will need to make judgements about the patterns, for example you may have to determine the direction of the movement on the screen, or you may have to indicate on which side of the screen you can see a shape. These tests will be carried out under a number of different light levels so that we can see how this affects your vision. When you do the tests under the lowest light levels we will first ask you to sit wearing dark goggles for 30 minutes to allow your eyes to adapt to the dark. During this time you can listen to music or a radio show. We will also ask you to wear dark glasses, similar to sun glasses, for some of the tests, to make it extra dark.

For the second session, we will place an EEG cap on your head. This is similar to a swimming cap but contains many small sensors that rest on the head and are able to pick up changes in brain activity. The cap is soaked in a salt solution to increase its conductivity so you may get a slightly wet scalp during the tests. This usually dries out over the course of the session but we will provide you with towels and a hairdryer if needed. Whilst wearing the EEG cap we will ask you to observe patterns on a computer screen, similar to those seen in the first session. While you view these we will record your brain activity.

The tests will take place within University College London, approximately 2 miles west of Moorfields Eye Hospital. We will usually refund travel expenses up to £50 per patient which can contribute towards public transport costs or petrol money (45p/mile) and parking.

What are the possible disadvantages or risks of taking part?

There are no known disadvantages or risks.

What are the possible benefits of taking part?

These investigations will provide detailed information regarding the functioning of the visual brain in people with cone dystrophies. The findings of this study will help gain a more accurate understanding of cone dystrophies and we hope that it will also be valuable in helping to develop future treatments.

What if something goes wrong?

The research does not carry any more risks than a normal visit to the hospital, or completing a routine vision test. If taking part in this research project harms you, there are no special compensation arrangements. If you are harmed due to someone's negligence, then you may have grounds for a legal action but you may have to pay for it. Regardless of this, if you wish to complain about any aspect of the way you have been approached or treated during the course of this study, the normal National Health Service complaints mechanisms will be available to you.

Will my information be kept confidential?

All information collected for the study will be kept strictly confidential. The research team will not pass on your personal details to anyone else.

What will happen to the results of the research study?

All the information from the study will be published in medical journals and presented to relevant health professionals at meetings and conferences. We would also be pleased to provide information about the results of the study to anyone who has taken part. Individual patients will not be identified in any reports or publications arising from the study.

Contacts for further information

For specific questions about the research, please contact either:

Investigator:	*Chief Investigator:*
Ms Eliza Burton	Dr Marko Nardini
UCL Institute of Ophthalmology	UCL Institute of Ophthalmology
Phone: 0207 608 6819	Phone: 0207 608 6909
Email: eliza.burton@ucl.ac.uk	email: m.nardini@ucl.ac.uk

Thank you for reading this and considering taking part in this study

UCL INSTITUTE OF OPHTHALMOLOGY
DEPARTMENT OF VISUAL NEUROSCIENCE

SUBJECT PAYMENTS AND EXPENSES

Name:

Address:

_____

Travel expenses:

Rail fare: £

Taxi fare: £

Other expenses:

Subject fees: £

Total: £

Subject's signature: _____ Date: _____

This is to confirm that the above-named participated as a subject in _____ project.

Signature: _____

APPENDIX II – LIST OF PRESENTATIONS

Presentations

Burton E. A. (2014). Biological Motion Perception. Talk given at the Dana Centre, Science Museum, London, UK. Public Engagement Event.

Burton, E A., Wattam-Bell, J., Nishiguchi, K. M., Sundaram, V., Webster, A., Moore, A., Michaelides, M., Nardini, M. (2013). Plasticity of cortical visual processing in atypical development: evidence from congenital achromatopsia. Poster presented at BPS Developmental Conference, Reading, UK.

Burton, E A., Wattam-Bell, J., Nishiguchi, K. M., Sundaram, V., Webster, A., Moore, A., Michaelides, M., Nardini, M. (2013). Development of global form, motion and biological motion processing in patients with congenital achromatopsia. Talk given at CVRS, Toronto, Canada**.**

Burton, E A., Wattam-Bell, J., Nishiguchi, K. M., Sundaram, V., Webster, A., Moore, A., Michaelides, M., Nardini, M. (2013). Cortical Vision in Congenital Achromatopsia. Talk given at ESLRR, Oxford, UK.

Burton, E A., Wattam-Bell, J., Nishiguchi, K. M., Sundaram, V., Webster, A., Moore, A., Michaelides, M., Nardini, M. (2013). Cortical visual processing in patients with congenital achromatopsia: form, motion and biological motion. Poster presented at VSS, Naples, Florida, USA.

Burton, E A**.**, Wattam-Bell, J., Nishiguchi, K. M., Sundaram, V., Webster, A., Moore, A., Michaelides, M., Nardini, M. (2012). Cortical visual processing in patients with congenital achromatopsia: form, motion and biological motion. Poster presented at VSS, Naples, Florida.

Burton, E A.**,** Wattam-Bell, J., Nishiguchi, K. M., Sundaram, V., Webster, A., Moore, A., Michaelides, M., Nardini, M. (2012). Cortical processing of form, motion and biological motion in patients with congenital achromatopsia. Poster presented at the AVA christmas meeting, UCL.

Burton, E A.**,** Wattam-Bell, J., Michaelides, M., Nishiguchi, K. M., Sundaram, V., Webster, A., Moore, A., Nardini, M. (2012). Coherent form, motion and biological motion perception in congenital achromatopsia. Talk given at ECVP, Alghero, Italy.

Burton, E. A**.**, Wattam-Bell, J., Nardini, M. (2012). The impact of optical blur on cortical responses to global form and motion. Poster presented at VSS, Naples, Florida.

Funding Awards

UCL Graduate School Major Travel Grant (2013)

APPENDIX III – BIOLOGICAL MOTION SSVEP

Introduction

Behavioural tests of biological motion are well documented and widespread (E.g. Ahlstrom, Blake, & Ahlstrom, 1997; Bardi, Regolin, & Simion, 2011; Blake, Turner, Smoski, Pozdol, & Stone, 2003; Freire, Lewis, Maurer, & Blake, 2006; Hadad, Maurer, & Lewis, 2011). However, EEG tests of biological motion perception are sparse and those that do exist have focussed on a transient design (Hirai & Hiraki, 2005; Hirai, Senju, Fukushima, & Hiraki, 2005; Reid, Hoehl, & Striano, 2006). In order to match the steady-state form and motion tests described in this thesis, a new biological motion VEP test was designed and piloted.

Materials and Methods

Participants

20 participants (mean age 34.2, standard deviation 7.9) completed a new pilot version of a biological motion VEP task. All participants had normal or corrected to normal vision and no known neurological conditions. Participants were recruited from the UCL Psychology Subject Pool as well as through word of mouth. All participants were given an information sheet and gave written informed consent before participating.

Stimuli Generation

The stimuli were generated as described in chapter 2, using Cutting's algorithm (Cutting, 1978). Stimuli consisted of a biological point light figure completing a walking motion in the centre of the display. The figure could appear at one of two randomised angles - either 90° or 180° so as to appear sideways on, walking either leftwards or rightwards. A central cross was present on the screen between trials which participants were asked to fixate.

Stimuli subtended 15.2 X 5.7°, the same size as was used in the behavioural experiment. The stimulus alternated between inverted and upright at a rate of twice per second (2Hz) (see

Figure *1*). 2Hz was selected as switching faster than this would not allow a full walking cycle. Inversion is a well-used method which causes the loss of biological motion perception while maintaining the same local motion cues.

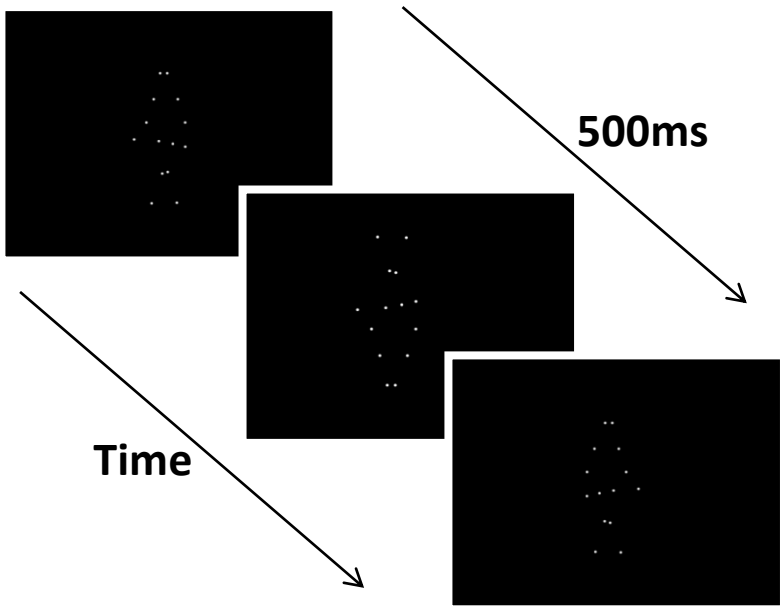

Figure 1. Example of the biological motion stimulus showing alternation between upright and inverted.

In addition participants also carried out the same experiment but all stimuli display were scrambled. Scrambled biological motion therefore alternated between upright and inverted at a rate of 2 Hz. This was done to assess whether any difference in response could be recorded to biological as opposed to scrambled motion.

Stimuli were generated within Matlab and displayed on an LG Flatron 915FT *Plus* CRT monitor, 60 Hz refresh rate, with a viewing distance of 60 cm.

Experimental design and procedure

Stimuli were viewed binocularly at a distance of 60 cm. Participants were instructed to remain as still as possible during the EEG recording. A fixation point was present in the

centre of the display throughout the experiment and participants were instructed to fixate this.

Participants completed two runs to the experiment. Each run consisted of 20 blocks each containing 10 stimulus cycles.

ssVEP recording

Recordings were made with the setup described in chapter 2 using a 128-electrode HydroCel Geodesic Sensor Net v1.0 (Electrical Geodesics Inc., Eugene, Oregon) with the vertex as the reference.

Data analysis

Data was analysed in Matlab(*MATLAB*, 2012) and SPSS (*PASW STATISTICS*, 2009).

Results

The raw F1 amplitude at each electrode in response to upright/inverted biological motion, averaged across the 20 participants, have been plotted in Figure 2. No clear pattern of activation can be seen in the topographic plot

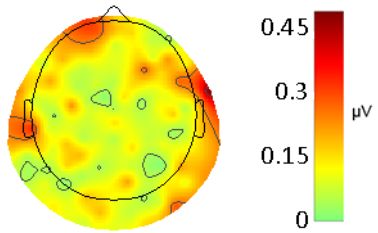

Figure 2. Raw F1 amplitude (μV) averaged across 20 participants.

Data from the 20 participants in response to upright/inverted biological motion was analysed using the T^2_{circ} statistic. No electrodes generated a significant T^2_{circ} response indicating that activation across the scalp was generated by noise and not tuned to the biological motion stimulus.

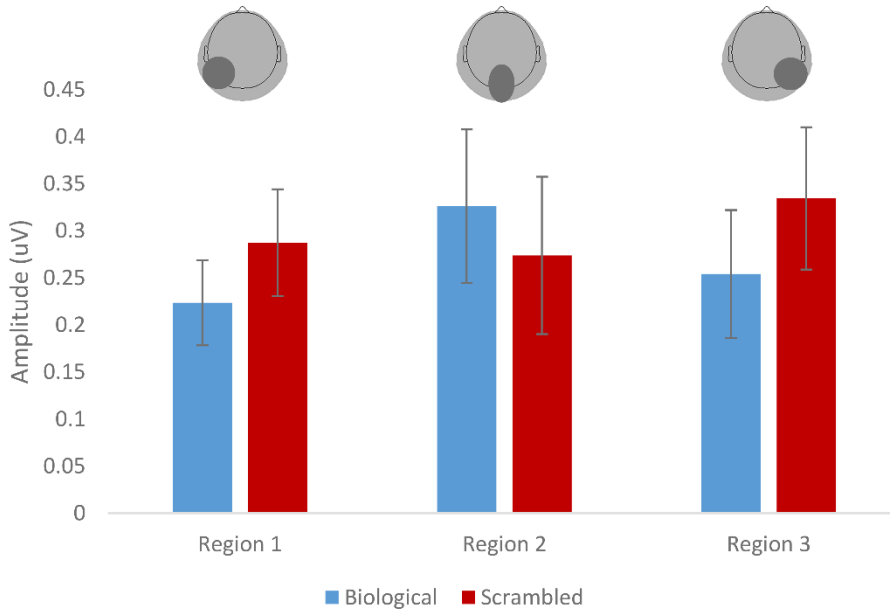

Figure 3. Amplitude data from biological and scrambled SSVEPs. Error bars represented the standard error of the mean.

Comparison between the F1 amplitudes in the scrambled and unscrambled experiments was carried out at 3 locations across the posterior scalp (see Figure 3). A repeated measures anova for the 3 regions found no significant effect of motion type (scrambled or biological); F(1,20) = 0.068, p = 0.797) and no significant effect of region (F(2,40) = 3.234, p = 0.06). There was also no interaction between motion type and region (F(2,40) = 0.038, p = 0.963). This suggests that the biological motion was unable to produce a discernible response at the three scalp locations.

Discussion

Steady-state biological motion stimuli were unable to generate a significant T^2_{circ} VEP response in 20 participants tested. There was also no significant difference between responses generated by scrambled vs. unscrambled biological motion at three posterior scalp locations.

Possible reasons for the results may lie in the rapid nature of a steady-state design being ill-suited to biological motion perception. The perception of a walking motion relies of analysis of complex temporal information. Although the stimulus used in the experiment contained a

full walking cycle this may have been insufficient to generate a strong perception of biological motion. The rapid inversion of the stimulus may have further detracted from the perception of biological motion.

Due to an absence of reliable SSVEP response in this experiment, biological motion VEPs were left out of the main experiments within this thesis.

APPENDIX IV – CSF PILOTING RESULTS

The qCSF method (Lesmes et al, 2010) was used to create a test of contrast sensitivity for use in this thesis. The method has been reviewed in a number of papers (Hou et al., 2010; Lesmes et al., 2010). In order to assess the functioning and reliability of the specific contrast sensitivity test designed for this project, the test was piloted on three participants (aged 20.5,27.4 and 28 years) who each completed three runs of the test. All participants had normal or corrected to normal vision and no known neurological conditions. Participants were recruited from members of staff within the UCL Institute of Ophthalmology.

Stimuli consisted of a Gabor patch, a sinusoidal grating, set in a Gaussian envelope with standard deviation set to a constant 6°, as described in the General Methods (chapter 2).

The test was able to present 23 spatial frequencies measured in CPD (0.56-13.76) and 25 contrast levels measured in Michelson contrast. 0.5%-97%. Spatial frequency and contrast were selected for each trial based on the qCSF method.

Gabors were presented 10° to the left or right of fixation. Gabors varied in spatial frequency and contrast from trial-to-trial based on the qCSF method. Stimuli were presented for 5 seconds and participants indicated with a button press whether the stimulus was to the right or left of fixation. After 100 trials the test ended and the contrast sensitivity function was mapped. Testing was carried out at 8.7 cd/m^2, the luminance used for the experiments described in chapters 4&5.

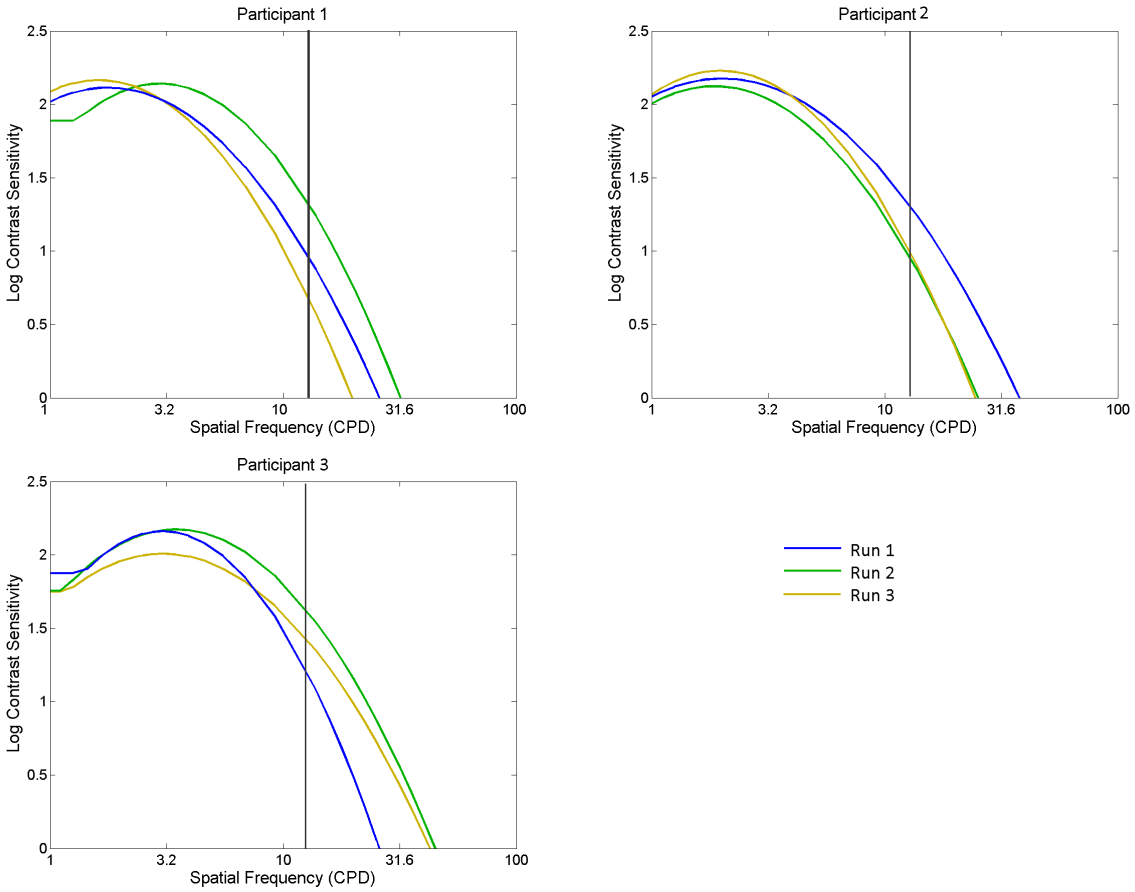

Figure 4. Contrast sensitivity functions for three participants across three 100 trial runs. Maximum spatial frequency presented was 13.75 cpd.

Figure 4 shows that participants had a high level of agreement between the three runs they completed. The cut-off spatial frequency had an average range of 27.2-32.9 cpd and peak contrast sensitivity ranged on average from 2.07-2.2 log CS.

The CSF test produced consistent results across three runs in three participants as well as between the three participants with low levels of variability. This indicates the test is able to generate reliable estimates of contrast sensitivity across individual runs.

APPENDIX V – BLUR CONTROL EXPERIMENT

In order to address whether global changes in the structure of the stimulus may have affected F2 responses, 5 participants from the blur experiment described in chapter 3 took part in an additional VEP experiment.

For half the experiment participants had VEP amplitudes recorded while viewing form and motion stimuli that alternated between 0% and 100% coherence (as used in the main experiment). For the other half, the form or motion stimuli each alternated between two random stimuli, both at 0% coherence. The order of testing was randomised for participants. Viewing conditions and experimental setup were all identical to those described in the main experiment.

Amplitude responses for F1 (global) and F2 (local) are shown in Figure 5. Amplitudes were taken from the regions of interest described in the main experiment. Conditions including coherent stimuli had significantly higher F1 amplitudes for both form and motion than did those with no coherence. A repeated measures ANOVA revealed a significant main effect of coherence ($F(1,4) = 15.05, p<0.01$). F2 amplitudes, however, did not vary significantly for coherent as compared with incoherent stimuli and no main effect of coherence was found ($F(1,4) = 0.189$, $p = 0.686$). F2 amplitude was not significantly affected by the presence or absence of coherent stimuli, indicating that these responses are to local changes in the stimulus display rather than to changes in global organisation.

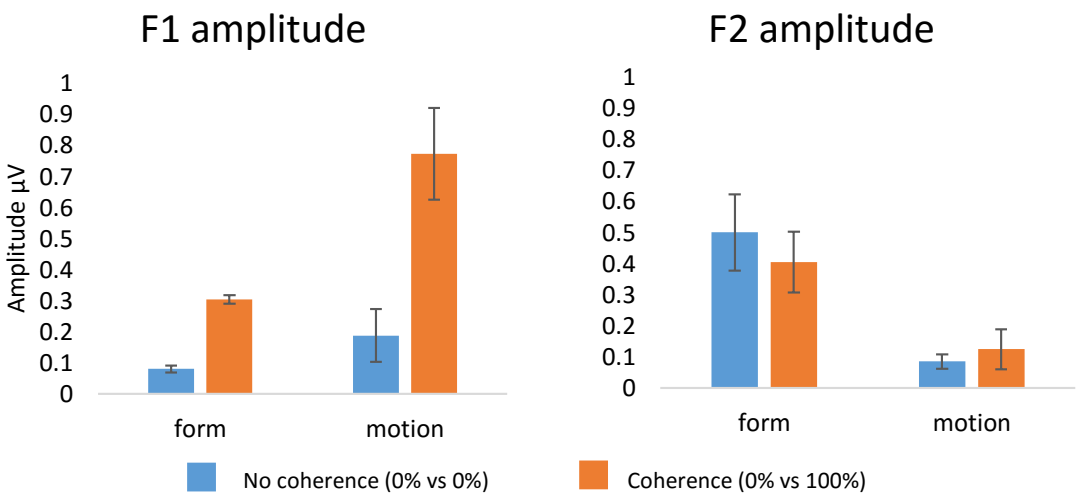

Figure 5. F1 and F2 amplitudes for form and motion stimuli. Blue bars represent responses to stimuli alternating between different 0% coherence stimuli. Orange bars represent responses to stimuli alternating between 0% and 100% coherence as used in the main experiment. Error bars represent the standard error of the mean.

APPENDIX VI - PUPIL SIZE DATA

		Photopic	High Mesopic	Low Mesopic	High Scotopic
FC	**Pupil**	5	5.5	6	6.5
	LogSTr	3.27	1.8	0.313366	-1.12
AR	**Pupil**	4	4.5	5	6
	LogSTr	3.08	1.62	0.19	-1.13
SK	**Pupil**	5	6	6.5	6.5
	LogSTr	3.27	1.79	0.38	-1.12
RA	**Pupil**	4.5	5	5.5	5.5
	LogSTr	3.18	1.64	0.24	-1.26
EB	**Pupil**	5	5.5	6.5	6.5
	LogSTr	3.27	1.72	0.38	-1.12

Table 1. Pupil size (mm) and Log Scotopic Trolands for 5 control participants in four light conditions.

		Photopic	High Mesopic	Low Mesopic	High Scotopic
S1	**Pupil**	4	4	5	6
	LogSTr	3.08	1.44	0.16	-1.19
S2	**Pupil**	3.5	4	4.5	4.5
	LogSTr	2.96	1.44	0.06	-1.44
S10	**Pupil**	4.5	5	6	6
	LogSTr	3.18	1.64	0.31	-1.19
S11	**Pupil**	4	4.5	4.5	5
	LogSTr	3.08	1.54	0.06	-1.34

Table 2. Pupil size (mm) and Log Scotopic Trolands (LogSTr) for 4 ACHM patients.

At retinal illuminance levels above 3 log scotopic trolands (logSTr), rods become saturated and cones take over, while the mesopic range is defined as falling between -1 and 2 logSTr and scotopic is below -1 LogST (Stockman & Sharpe, 2006). All participants (controls and patients) demonstrated LogSTr values within the appropriate luminance range with the exception of patient S2. S2 demonstrated retinal illuminance just short of the photopic range at 2.96 STr due to a smaller pupil in this condition than the other patients.

APPENDIX VII – ADDITIONAL CONE DISORDER DATA

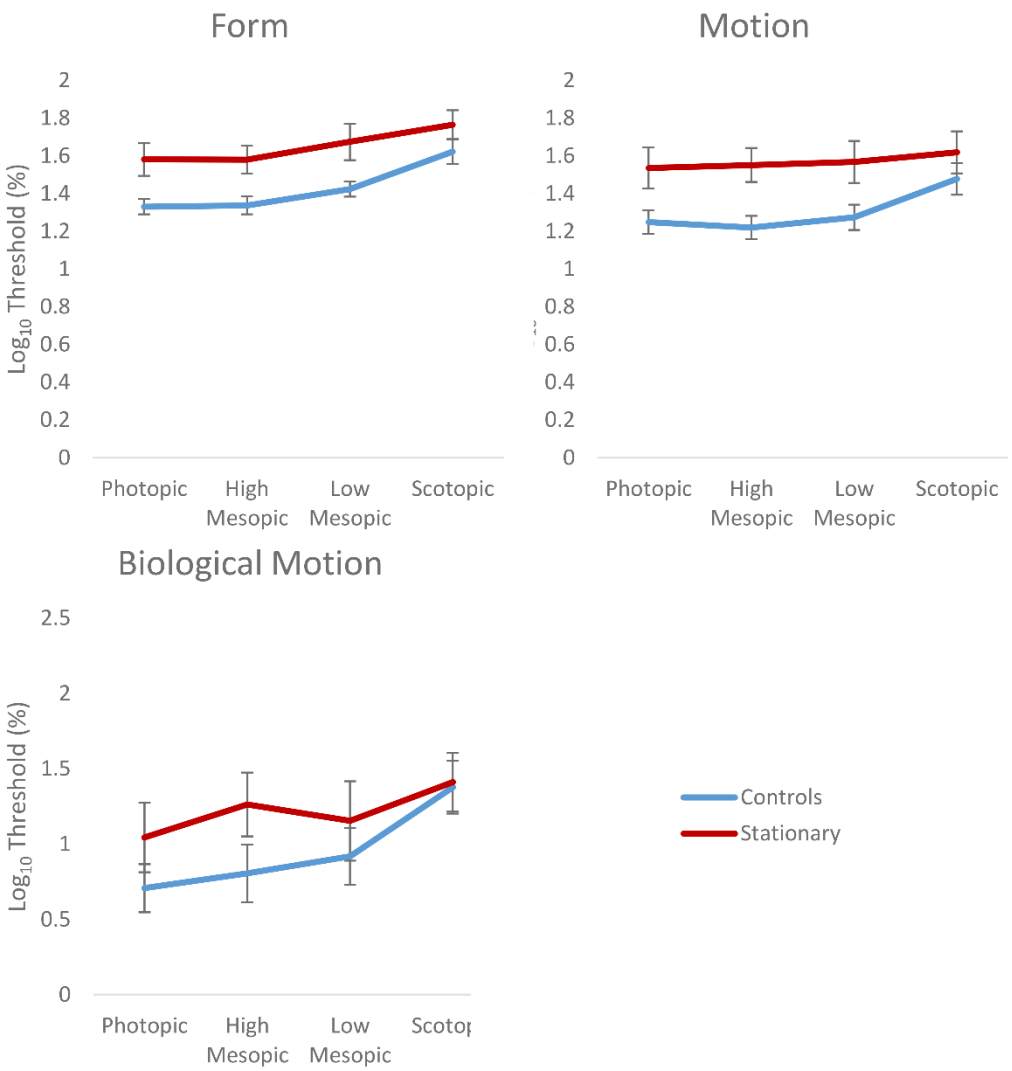

Figure 6. Form, motion and biological motion thresholds for controls and stationary patients across all four light levels tested. Error bars represent 95% confidence intervals.

	Form				Motion				Biological Motion			
	P	HM	LM	S	P	HM	LM	S	P	HM	LM	S
P1	1.43	1.40	1.71	1.86	1.35	1.24	1.34	1.57	1.21	1.38	1.30	1.81
P2	1.79	1.59	1.53	1.85	1.50	1.44	1.48	1.90	1.20	0.89	1.10	1.94
P3	1.51	1.58	1.74	1.95	1.68	1.64	1.65	1.94	1.34	1.83	1.76	1.98
P4	1.77	1.53	1.62	1.90	1.62	1.38	1.33	1.79	1.44	0.84	1.46	1.98
P5	1.49	1.49	1.62	1.87	1.42	1.27	1.40	1.58	1.78	1.60	1.70	1.69

Table 3. Form, motion and biological motion log thresholds for the 5 progressive patients. Results are given for each of the four light levels (photopic (p), high mesopic (hm), low mesopic (lm) and scotopic (s)).

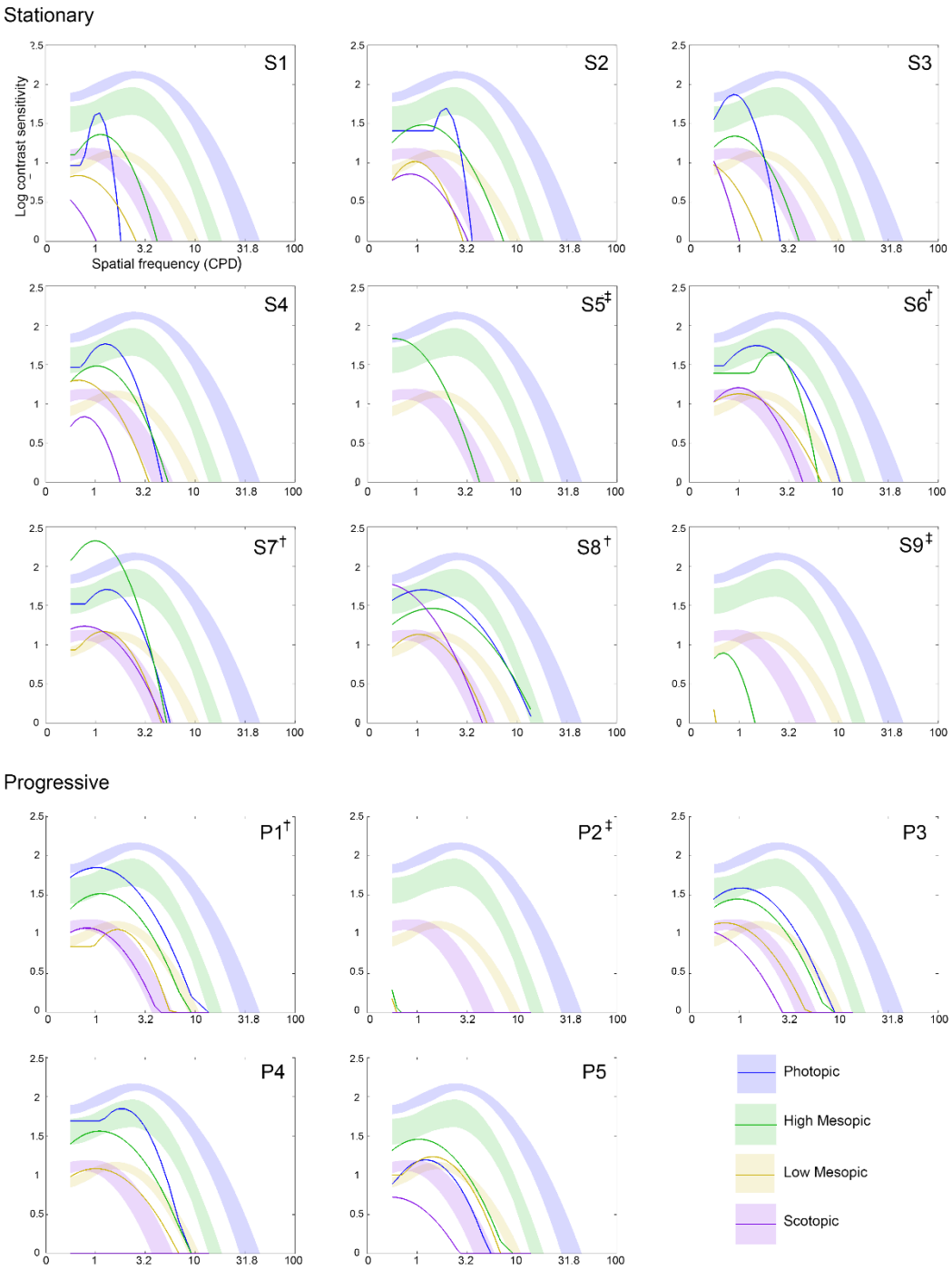

Figure 7. Contrast sensitivity functions for individual stationary and progressive patients across all four light levels tested. Solid lines represent CSFs for each light condition. Shaded areas represent the 95% confidence intervals of control data. Patients with CSFs within the normal scotopic range are marked †. Those who could not complete all conditions are marked ‡.

APPENDIX VIII – PROGRESSIVE CONE DYSTROPHY VEP TOPOGRAPHIES

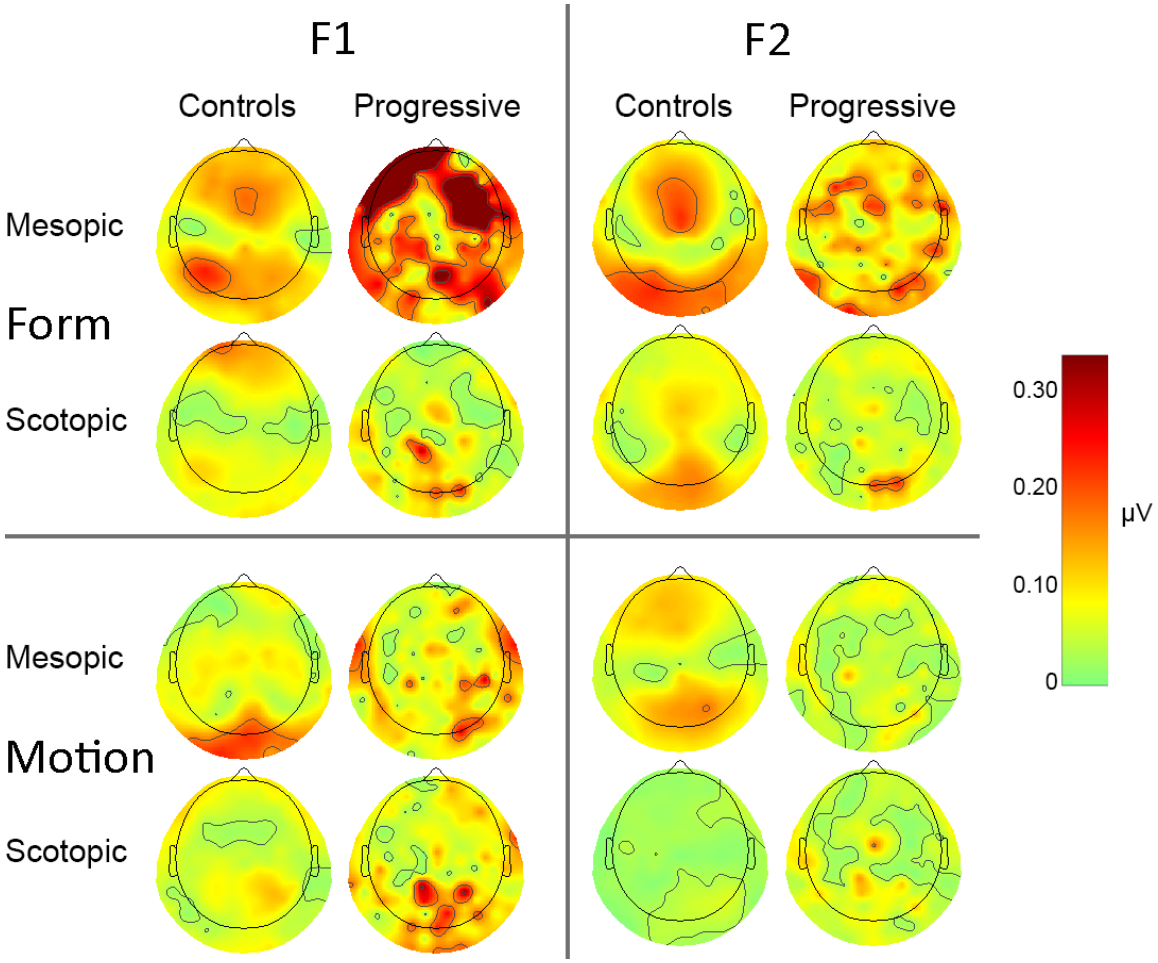

Figure 8. Topographic plots of average form and motion amplitudes (μV) for controls and progressive patients. Plots are shown for mesopic and scotopic conditions. F1 (global) and F2 (local) amplitudes have been plotted separately.