Radial Deformation Acuity In Children With Amblyopia

by

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Submitted in partial fulfillment of the requirements
for the degree of Master of Science

at

Dalhousie University
Halifax, Nova Scotia
March 2013

DALHOUSIE UNIVERSITY

DEPARTMENT OF CLINICAL VISION SCIENCE

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Date March 25, 2013

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DALHOUSIE UNIVERSITY

DATE: March 25, 2013

AUTHOR: Michael John Betts

TITLE: Radial Deformation Acuity In Children With Amblyopia

DEPARTMENT OR SCHOOL: Department of Clinical Vision Science

DEGREE: MSc CONVOCATION: MAY YEAR: 2013

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Dedication Page

I dedicate this paper to my incredible wife Anna. As I said to you on our wedding day, “I could never have achieved what I have or become the man I am, without your love and support. You truly have made me a better person”. I love you.

I would like to dedicate this to my son Nate. I can’t believe how lucky I am to have you in my life. You bring your mother and I so much joy. I hope this achievement inspires you to reach for whatever your dreams may be. I love you “Little Goose”.

To my unborn daughter, you will arrive exactly 22 days after I defend my thesis. I can’t wait to meet you. Daddy loves you so much already!

I would like to dedicate this to my parents. You always told your children that they could do anything if they put their minds to it. You helped us to dream big and you supported us financially when we needed you. You listened and laughed every time I sat down with you and said, “What am I going to do with my life?”. You made major sacrifices to ensure we became good kids. Dad, you showed us that if you work hard enough, you could accomplish anything. I try to take that approach in everything I do. Hopefully, I can set the same example for my children.

Finally, I would like to dedicate this to my grade eleven Chemistry teacher Mrs. Bryson. One day during class you asked me if I was illiterate or just stupid when I was struggling to understand the topic you were teaching. Well, Mrs. Bryson, I guess I’m neither.

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Abstract

Purpose: To examine the relationship between visual acuity (VA) and radial deformation acuity (RDA) in children 6 to 12 years of age with amblyopia.

Methods: RDA was measured in 35 participants with the Manchester RDA charts. VA was measured with the Early Treatment Diabetic Retinopathy Research Study (ETDRS) chart.

Results: Median VA in non-amblyopic and amblyopic eyes was 0.04 logMAR (IQF -0.06 – 0.12) and 0.24 (IQF 0.12 – 0.04), respectively (Wilcoxon Signed Ranks test, $z = -5.07$, $p < 0.001$). Median RDA in non-amblyopic and amblyopic eyes was 2.73 log (IQF 2.53 – 2.87) and 2.63 log (IQF 2.53 – 2.77), respectively (Wilcoxon, $z = -2.56$, $p < 0.05$). Spearman correlation suggested that the amblyopic deficits in VA and RDA were related, $r = -0.42$, $p < 0.05$.

Conclusion: A deficit in RDA was present in most children with amblyopia. A moderate relationship was noted between the amblyopic deficits found in VA and RDA.

List Of Abbreviations And Symbols Used

BEO	Both Eyes Open
cpd	Cycles per Degrees
CS	Contrast Sensitivity
DVD	Dissociated Vertical Deviation
ET	Esotropia
ETDRS	Early Treatment Diabetic Retinopathy Study
fMRI	Functional Magnetic Resonance Imaging
HT	Hypertropia
HypoT	Hypotropia
MAR	Minimum Angle of Resolution
MD	Monocular deprivation
RDA	Radial Deformation Acuity
Rx	Refractive error
sec. of arc	Seconds of Arc
VA	Visual Acuity
W4D	Worth Four Dot
XT	Exotropia
yrs	Year(s)

Glossary

Amblyopia: A unilateral or, less commonly, bilateral reduction of best corrected visual acuity that occurs in the setting of an otherwise normal eye, or a structural abnormality involving the eye or visual pathway, with reduction in visual acuity that cannot be attributed only to the effect of the structural abnormality. Often the fellow eye is not normal but has subtle defects. Diagnosis of amblyopia is based on asymmetry of visual acuity (a interocular difference of 2 lines on a logMAR visual acuity chart). Other visual functions such as contrast sensitivity and hyperacuity can also be affected. Amblyopia is traditionally classified in terms of the disorder or disorders that caused its occurrence (i.e. strabismic, refractive, or visual deprivation).

Anisometropia: A condition in which the two eyes have unequal refractive errors (interocular difference of ≥1 diopter).

Anisometropic amblyopia: A condition that develops when unequal refractive error in the two eyes causes the image on one retina to be chronically more defocused than the fellow eye. Greater amounts of anisometropia or astigmatism result in a greater risk and severity of amblyopia.

Astigmatism: A refractive error caused by the non-spherical (toroidal) surface of the cornea, lens, or both.

Bilateral refractive (ametropic) amblyopia: A form of refractive amblyopia that results in a bilateral reduction in acuity in both eyes of a young child. Its mechanism involves the effect of blurred retinal images alone in a patient who has had their bilateral high hyperopia or astigmatism left uncorrected.

Contrast sensitivity: Ability to detect detail having subtle gradations in grayness between test target and background.

Contrast threshold: The amount of contrast required to identify a target.

Critical or Sensitive period: The period during which deprivation is effective due to heightened plasticity, rather than the initial period of development or period during which recovery can be obtained.

Heterotropia: a manifest deviation not controlled by fusion. Also known as strabismus or squint.

Hyperacuity: Refers to a variety of vision tasks that involve sensing the direction or spatial offset of a line or point relative to a reference.

Mixed amblyopia: A combination of anisometropia and strabismus resulting in amblyopia.

Occlusion amblyopia: A specific form of deprivation amblyopia that may be seen after therapeutic patching or prolonged unilateral atropinization.

Neural plasticity: The ability of the central nervous system to change in response to experience. Specific patterns of input and/or experience can produce either temporary or permanent changes.

Radial Deformation Acuity: The ability to detect subtle distortions of a circular shape.

Refractive amblyopia: Amblyopia resulting from either untreated anisometropia or high bilateral refractive errors.

Strabismus: A misalignment of the two eyes that can be manifest, intermittent, or latent. When manifest, one fovea is not directed at the same object as the other. Also known as a squint, heterotropia, tropia or deviation.

Strabismic amblyopia: Amblyopia caused by a constant, non-alternating or unequally alternating tropia.

Threshold: The weakest size or intensity of a target that can be detected by an individual.

Visual acuity: A quantifiable limit of spatial discrimination.

Visual deprivation amblyopia: Amblyopia caused by complete or partial obstruction of the ocular media, resulting in disuse or understimulation of the retina. Can be caused by congenital or early onset cataract, corneal opacities, infectious or noninfectious intraocular inflammation, vitreous hemorrhage, and ptosis.

Acknowledgements

I would like to thank my supervisors Karen McMain and Dr. Paul Artes for all of their help, support and encouragement. I have learned so much from you. I would like to thank Patricia Pontbriand for her help in identifying suitable participants for my study. I would like to thank Vicky Dixon for her help in organizing appointments with my participants. I would like to thank Francois Tremblay for his assistance and support. Your willingness to chat and give feedback at a moments notice was very helpful. I would like to thank Erik Hahn. Your moral support and frequent verbal "kicks in the butt" helped me to finish this project. I would like to thank Leah Walsh for constantly encouraging me to finish my thesis. I always appreciated your support and encouragement. I would like to thank "The Man with all of the Answers", Steve Van Iderstine. Whenever I had a research related question, you were the person I would look to. I really appreciate all of the help you have given me over these past few years. I would like to thank my beautiful wife, wonderful son, unborn daughter, and parents for all of your support and love. Finally, I would like to thank Sensei Gerald Sanders, Sensei Ray McKinnon, Tammy Mosher and all of my training partners from Bushido Kai Martial Arts Academy. You were the outlet for all of my pent up frustration and stress over the past few years. I could not have reached this point without all of your help. Sorry for any bruises.

Chapter I: Introduction

Amblyopia is the most common treatable cause of decreased vision in children and yet remains one of the leading causes of decreased vision in adults (Levi, 2010). The diagnosis of amblyopia and decisions regarding treatment in literate patients are based on the results of optotype visual acuity (VA) testing. Additionally, VA is the primary outcome measure of amblyopia in the treatment literature. The VA chart considered to be the "gold standard" for VA assessment in most clinical trials is called the Early Treatment Diabetic Retinopathy Study VA chart (ETDRS) (Kaiser, 2009). With this said, both researchers and clinicians have identified a number of problems with the chart that affects the treatment of patients with amblyopia.

The ETDRS has good test-retest variability (TRV), however the sensitivity to detect changes in VA at 0.10 logMAR is poor (Rosser, Cousens, Murdoch, Fitzke, & Laidlaw, 2003). This means that a 2-line (10 optotype) change in VA is required for a change in VA to be considered clinically significant. This is a large difference and consequently, the EDTRS chart may not be sensitive enough to detect small changes in VA during amblyopia treatment. This is problematic for those patients who appear to have reached a plateau in VA during treatment or who have reached equal VA, discontinued treatment, and subsequently suffered a regression of acuity. The second issue, is that the use of only 5 letters per line on the ETDRS chart increases the possibility of false recognition due to guessing driven by the forced choice method (Ricci, Cedrone, & Cerulli, 1998).

Clinicians and researchers have concerns that the use of VA alone to monitor amblyopia treatment may be insufficient. A number of authors have noted that amblyopia is not a single abnormality that can be completely characterized by a deficit in VA

(McKee, Levi, & Movshon, 2003; Simmers, Gray, McGraw, & Winn, 1999). VA represents only one type of visual capacity (i.e. recognition of small black letters on a bright white background). Amblyopia can also result in monocular fixation preference, eccentric fixation, as well as impairments in other visual thresholds such as contrast sensitivity (CS), stereopsis, and positional uncertainty (hyperacuity) (Cuiffreda, Levi, & Selenow, 1991; Hess, 2001; Simmers et al., 1999). Furthermore, some authors have suggested that amblyopia does not affect each visual function equally and while treatment may show little or no improvement in VA, there may still be changes occurring in the other visual functions that are not being monitored (Simmers et al., 1999). Consequently, it is important that clinicians understand the diverse reduction in visual performance that occurs in amblyopia and the need to monitor other aspects of visual function during the treatment of amblyopia.

Hess (2001) and Hess, Wang, Demanins, Wilkinson, & Wilson (1999) have suggested that the dominant feature of the perceptual deficit in amblyopia is positional uncertainty (hyperacuity), rather than VA or CS. Human observers show astonishingly high performance with hyperacuity tasks, with up to 10 times better thresholds compared to standard VA (Westheimer, 1975). It is now well established that amblyopes demonstrate deficits in a variety of hyperacuity tasks (Birch & Swanson, 2000; Cox, Suh, & Leguire, 1996; Harvey, Dobson, Miller, & Clifford-Donaldson, 2007; Levi, Polat, & Hu, 1997; Levi & Klein, 1982b; McKee et al., 2003; Simmers et al., 1999). Previous research by McKee et al. (2003) found that vernier acuity, a more common variety of hyperacuity task was highly correlated with VA and that the loss of the former was highly correlated with the latter. Consequently, vernier acuity testing has not become commonplace in clinical practice as the results of one test could be predicted from the

other. Another form of hyperacuity, radial deformation acuity (RDA), has been shown to be severely affected in adults with strabismic amblyopia and thus may be useful in the diagnosis of amblyopia and the monitoring of its treatment (Hess et al., 1999).

To date, only one study has examined the relationship between VA and RDA (Subramanian, Morale, Wang, & Birch, 2012). Unfortunately, this study only included strabismic amblyopes and had a small sample size, thus limiting its generalizability to other forms of amblyopia. Consequently, the present study sought to examine the relationship between RDA, LogMAR VA, and CS in a group of functional amblyopes recruited from a "real world" pediatric ophthalmology practice.

1.1.1 Purpose

The purpose of the present study was to examine the effect of amblyopia on RDA in patients at the IWK Health Centre. Types of amblyopia included strabismic, anisometropic, and mixed (anisometropia and strabismus in the same patient).

1.1.2 Study Objectives And Hypothesis

The objective of the present study was to examine the relationship between VA and RDA in 35 children with amblyopia. The hypothesis of this research was that RDA deficits in amblyopic eyes (compared to the fellow eye) were related to the deficits in VA. The research questions included:

1) How does RDA compare to optotype VA in children with amblyopia?
2) How does RDA compare to CS in children with amblyopia?
3) How does age affect RDA in children with amblyopia?
4) Can children 6 to 12 years of age complete the Manchester RDA test?
5) What is the test-retest variability (TRV) of the Manchester RDA test in children with amblyopia?

Chapter II: Review Of Literature

2.1 Amblyopia

2.1.1 Definition

The term amblyopia comes from the Greek word meaning “dullness of vision” or “blunt sight” and has been recognized as a clinical disorder for more than 300 years (Daw, 1998; Flynn, 1991; Lampert, Cox, & Burke, 2002; Mittelman, 2003). It is a form of cerebral visual impairment characterized by abnormal neuronal numbers and connections in the visual pathway and cortex. In general, amblyopia is believed to be the result of disuse from inadequate foveal or peripheral retinal stimulation and/or abnormal binocular interaction that causes different input from the foveas.

Amblyopia can be defined as a unilateral or bilateral reduction of best-corrected VA that occurs in an otherwise normal eye, or a structural abnormality involving the eye or visual pathway, with reduction in VA that cannot be attributed only to the effect of the structural abnormality (Hoyt, 2005; Wong, 2012). In some patients, the fellow eye or non-amblyopic eye can also have subtle defects (Simons, 2005). The damage produced by amblyopia is most often expressed as a reduction in VA in a healthy eye despite optical correction (Levi, 2010). With this said, evidence is accumulating that shows amblyopia can result in a broad range of neural, perceptual, oculomotor, and clinical abnormalities (Levi, 2012).

The diagnosis of amblyopia is most often based on a two-line difference or more in best-corrected VA between the eyes on a logMAR optotype VA chart (American Academy of Ophthalmology Pediatric Ophthalmology and Strabismus Panel, 2007). With this said, some research literature defines amblyopia as a reduction in best-corrected

visual acuity to less than 6/9 monocularly on a Snellen optotype VA chart (Kanonidou, 2011).

2.1.2 Classification

Amblyopia is caused by an abnormal visual experience early in life and the resultant deficits can vary in degree of loss (Levi, 2010). Amblyopia is most often associated with an early history of abnormal visual experience including binocular misregistration (strabismus), image degradation (high refractive error and anisometropia, astigmatism) or both (mixed strabismic and anisometropic), and less commonly, with visual deprivation (congenital cataract or ptosis) (Levi, 2010; Wong, 2012). Amblyopia has traditionally been classified in terms of the disorder responsible for its occurrence. These include:

1. Strabismic amblyopia: This occurs as the result of a constant, non-alternating or unequally alternating heterotropia. This form of amblyopia occurs more often in esotropes than in patients with exotropia or hypertropia (von Noorden & Campos, 2002). Strabismic amblyopia is thought to result from competitive or inhibitory interaction between neurons carrying the non-fusible inputs from the two eyes. This leads to domination of cortical vision centers by the fixating eye and chronically reduced responsiveness to input by the non-fixing eye (Daw, 2009).
2. Refractive amblyopia: This occurs as a result of either untreated anisometropia or high bilateral refractive errors. Anisometropic amblyopia develops when unequal refractive error in the two eyes causes the image on one retina to be chronically more defocused than the fellow eye (American Academy of Ophthalmology Pediatric Ophthalmology and Strabismus Panel, 2007; Kanonidou, 2011).

Anisometropic amblyopia is thought to result partly from the direct effect of image blur on the development of visual acuity in the involved eye and partly from interocular competition or inhibition similar to that responsible for strabismic amblyopia (American Academy of Ophthalmology Pediatric Ophthalmology and Strabismus Panel, 2007). Levi (2010) suggests that the severity of the amblyopia appears to be associated with the degree of refractive imbalance between the two eyes. Finally, anisometropic amblyopia can occur in combination with strabismus resulting in a mixed form of amblyopia (Levi, 2010; Wong, 2012).

Bilateral refractive (ametropic) amblyopia is a less common form of refractive amblyopia that results in a bilateral reduction in acuity in both eyes of a visually immature child. Its mechanism involves the effect of blurred retinal images alone in a patient who has had their bilateral high hyperopia or astigmatism left uncorrected (American Academy of Ophthalmology Pediatric Ophthalmology and Strabismus Panel, 2007).

3. Visual deprivation amblyopia is caused by complete or partial obstruction of the ocular media, resulting in disuse or understimulation of the retina (American Academy of Ophthalmology Pediatric Ophthalmology and Strabismus Panel, 2007; Kanonidou, 2011). The most common cause is a congenital or early onset cataract, but deprivation amblyopia can also result from corneal opacities, infectious or noninfectious intraocular inflammation, vitreous hemorrhage, and ptosis. Deprivation amblyopia is the least common form of amblyopia but the most severe and difficult to treat (American Academy of Ophthalmology Pediatric Ophthalmology and Strabismus Panel, 2007). Amblyopic visual loss resulting

from a unilateral obstruction within the pupil tends to be worse than that produced by bilateral deprivation of similar degree because interocular competition adds to the direct developmental impact of severe image degradation (American Academy of Ophthalmology Pediatric Ophthalmology and Strabismus Panel, 2007; von Noorden & Campos, 2002). In the unilateral cases, the amblyopia is also accompanied by a secondary sensory esotropia or exotropia. Even in bilateral cases, however, visual acuity can be significantly reduced (20/200 or worse).

Occlusion amblyopia is a specific form of deprivation amblyopia that may be seen after therapeutic occlusion, or optical or pharmacologic penalization. Penalization can be defined as blurring of the non-amblyopic eye to force fixation with the amblyopic eye (Tejedor & Ogallar, 2008).

2.1.3 Prevalence

Amblyopia is the most common treatable cause of monocular blindness with a prevalence ranging from 1-6% in the population worldwide (Choong, Lukman, Martin, & Laws, 2004; Hrisos, Clarke, & Wright, 2004; Rahi, Logan, Timms, Russell-Eggitt, & Taylor, 2002; Searle, Norman, Harrad, & Vedhara, 2002). Untreated amblyopia is a barrier to certain occupations, affects binocular vision and stereopsis, impairs the ability to carry out many visually demanding tasks, and may interfere with a child's educational progress and sporting ability (Rahi et al., 2002; Searle, Vedhara, Norman, Frost, & Harrad, 2000; Searle et al., 2002). Furthermore, people with amblyopia are at greater risk from blindness than those with two good eyes as a result of injury or disease in the non-amblyopic eye with the lifetime risk of serious bilateral vision loss being 1.2-3.3% (Rahi

et al., 2002). Patients with amblyopia make up a large segment of the patient population in pediatric ophthalmology.

2.1.4 Neural Mechanism Of Amblyopia

The site of damage in amblyopia has been a longstanding question. Very little was known about the neural mechanisms of amblyopia until the pioneering studies of David Hubel and Torsten Wiesel in the 1960s. Their Nobel Prize winning work conducted on cats and then later on monkeys, generated the first insights into the neural basis for amblyopia. Hubel and Wiesel studied the effects of monocular deprivation (MD) produced by lid suture and artificial strabismus on the structure and function of the visual system (Daw, 2009; Hubel & Wiesel, 1998). The three major conclusions from their research were: 1) The primary site of abnormality in amblyopia is at the level of the primary visual cortex (striate cortex, V1, Broadman's area 17); 2) Identified and established the concept of the critical (or sensitive) period for monocular deprivation; 3) Demonstrated that competition between afferent inputs between the two eyes is responsible for some of the synaptic changes following abnormal visual experience early in life. The finding that the adverse effects of MD were much greater than those produced by binocular deprivation supported this final conclusion (Hubel & Wiesel, 1998).

Although the work of Hubel and Wiesel was considered groundbreaking, significant debate about the neural basis and site of the amblyopic deficit continue to this day. It is now thought that there are no significant anatomic or physiologic abnormalities in the retina or lateral geniculate nucleus (LGN) of amblyopes (Barrett, Bradley, & McGraw, 2004; Hess, 2001; Wong, 2012). With that said, Levi (2010) suggests that it is possible that retrograde degeneration may affect the LGN (where there is some shrinkage of cells in the parvocellular layers) and retina, although it is unlikely that these effects

contribute significantly to the behavioral losses. Current opinion is that the earliest functional and anatomic abnormalities that contribute significantly to the behavioral losses in amblyopia occur in the striate cortex (V1) (Barrett et al., 2004; Hess, 2001; Wong, 2012). A review by Wong (2012) further notes that there are abnormalities in downstream extrastriate and later specialized cortical areas, many of which are not acuity limited. Of particular interest to the present study are the findings of extrastriate deficits in global form perception, global contour perception, Vernier acuity and positional acuity (Barnes, Hess, Dumoulin, Achtman, & Pike, 2001; Chen, Norcia, Pettet, & Chandna, 2005; Dallala, Wang, & Hess, 2010; Levi, Yu, Kuai, & Rislove, 2007). Currently, it is unknown whether the extrastriate deficits are selective deficits unrelated to the known striate deficit, or simply an amplification of the earlier loss (Barrett et al., 2004).

2.1.5 Critical Period In Amblyopia

The term "critical period" (or "sensitive period") came into common use after the publication of Wiesel and Hubel's research on monocular deprivation (Daw, 1998). The critical period refers to the period during which deprivation is effective due to heightened plasticity, rather than the initial period of development or period during which recovery can be obtained (Daw, 1998). Plasticity refers to the ability of the central nervous system to change either temporarily or permanently, in response to experience (Vida, Vingilis-Jaremko, Butler, Gibson & Monteneiro, 2011). The critical period depends on the anatomical level of the system being studied with cells at higher levels of the system having a longer critical period. Furthermore, there appear to be different critical periods for different visual functions (Lewis, 2005). At the end of the critical period, plasticity decreases significantly.

The age at which children are most susceptible to amblyopia is during the first 2-3 years of life. This sensitivity gradually decreases until the child reaches 6 or 7 years of age, when visual maturation is complete and the retinal cortical pathways and visual centers become resistant to abnormal visual input (Lampert et al., 2002; Levi, 2005). The time frame for amblyopia therapy has traditionally been aligned with the critical period because it was thought that plasticity ended with the conclusion of the critical period. Consequently, it has been uncommon for amblyopia treatment to be attempted once visual maturity has been reached. Interestingly, a number of articles suggest that recovery from amblyopia can occur after visual maturity indicating that the visual system may retain some plasticity into adulthood (Hess, Mansouri, & Thompson, 2010; Levi et al., 1997; Levi & Polat, 1996; Levi, 2005; Rahi et al., 2002). Clearly, more research needs to be done to understand the critical periods in amblyopia as well as determine the optimum treatment methodology for amblyopia.

2.1.6 Clinical Features

Although amblyopia is most often discussed in terms of reduced monocular VA, there are a number of other clinical features associated with the disorder. These include crowding phenomenon, reduced CS, reduced or absent stereopsis, positional uncertainty, distortions in the shape of a stimulus, motion deficits, monocular fixation preference, and eccentric fixation (Daw, 1998; Lampert et al., 2002). Interestingly, one study suggested that strabismic, anisometropic and mixed forms of amblyopia have different patterns of visual losses in acuity (VA, vernier, and grating) and CS. McKee et al. (2003) found that strabismic amblyopes performed more poorly on pattern acuity tasks (vernier and optotype acuity) and had better than normal CS at low spatial frequencies. Anisometropic amblyopes tended to have moderate acuity loss and poor CS. Mixed amblyopia was

associated with very poor acuity and normal or subnormal CS. These authors also found that residual binocular function was a major determinant of the pattern of visual deficits. They found that those with no residual binocular function had poorer acuity but better CS, whereas those with residual binocular function tended to have better acuity but poorer CS.

Some authors have also speculated that the fellow eye of amblyopes is abnormal. A literature review by Simons (2005) identified a number of abnormalities in strabismic amblyopes including small deficiencies in VA, vernier acuity, global motion processing, contrast sensitivity, pupil response latency, along with small amounts of fixational eccentricity, unsteady fixation, increased VEP latency in the presence of normal VA, subnormal scotopic sensitivity and dark adaptation. This author also reported in both strabismic and anisometropic amblyopia that the fellow eye had deficits in CS, detection of Gabor-patch-based contours, and in the ability to detect motion defined forms.

2.1.7 Clinical Evaluation

The initial amblyopia evaluation includes a comprehensive ophthalmic exam with attention to risk factors including strabismus, anisometropia, family history of strabismus or amblyopia, and the presence of a media opacity or structural defect (American Academy of Ophthalmology Pediatric Ophthalmology and Strabismus Panel, 2007). The eye examination can include binocularity/stereopsis testing, assessment of fixation pattern and monocular VA, binocular alignment and ocular motility, pupil examination, external examination, anterior segment examination, cycloplegic retinoscopy, and fundus examination.

The damage produced by amblyopia is generally expressed in the clinical setting as a loss of VA in an apparently healthy eye, despite appropriate optical correction. The severity of amblyopia is associated with the degree of imbalance between the two eyes

and at the age at which the amblyogenic factor occurred (Levi, 2010). Consequently, the diagnosis of amblyopia requires the detection of a VA deficit and identification of a likely cause. In literate patients, a diagnosis of amblyopia requires a ≥ 2-line interocular difference (10 optotypes) in best-corrected VA (American Academy of Ophthalmology Pediatric Ophthalmology and Strabismus Panel, 2007). In preliterate patients, the VA deficit can be defined as asymmetric objection to monocular occlusion and/or failure to initiate or maintain fixation with one eye.

2.1.8 Treatment

Amblyopia can be reversed or eliminated when diagnosed and treated early in life (Levi, 2010). Unfortunately, the rate of success declines with advancing age. Failure or lack of treatment can result in lifelong visual loss and may cause difficulties later in life for the patient. Timely treatment can improve VA and in some cases, binocularity, as well as decrease the chance of severe handicap if there is a loss of vision in the fellow eye later in life (Rahi et al. 2002).

The treatment of amblyopia involves attempting to improve the patients VA by using one or more of the following strategies (American Academy of Ophthalmology Pediatric Ophthalmology and Strabismus Panel, 2007). The first is to address the cause of visual deprivation. The second is to correct any significant refractive error. The third is to force the patient to use the amblyopic eye by penalizing the fellow eye. The goal of treatment is to achieve equal VA between the two eyes. If this is not possible, the goal is to maximize amblyopic eye VA. The choice of treatment is based on the child's age, VA, and adherence with previous treatment as well as the child's physical, social, and psychological status. Choice of therapy also depends on the primary cause of amblyopia. Amblyopia is most often treated with patching but can also be treated using optical

correction, pharmacological penalization, optical penalization, Bangerter filters, and surgery to treat the cause of the amblyopia (cataract). Other less common treatments include acupuncture and vision therapy (American Academy of Ophthalmology Pediatric Ophthalmology and Strabismus Panel, 2007).

2.2 Visual Acuity

2.2.1 Definition

VA refers to a quantifiable limit of spatial discrimination and is an essential part of the ophthalmic examination (Cuiffreda et al., 1991; Westheimer, 2009). VA is a highly complex function that consists of the minimum separable (hyperacuity), minimum visible, and minimum resolvable (ordinary visual acuity) (Adler, 1987; Cassin, 1995). Minimum separable refers to a variety of tasks that involve sensing the direction or spatial offset of a line or point relative to a reference (Kniestedt & Stamper, 2003). The eye is capable of subtle discrimination in spatial localization and can detect misalignment of 2 line segments in a frontal plane if these segments are separated by as little as 3 to 5 seconds of arc (Kniestedt & Stamper, 2003; Westheimer, 1975; Westheimer, 1979). Minimum visible is a light discrimination function. It includes brightness sensitivity and brightness discrimination. Minimum visible is concerned with the ability to detect a small difference in the brightness of two light sources. It determines the presence or absence of a visual stimulus against a background (Cuiffreda et al., 1991; Kniestedt & Stamper, 2003; Westheimer, 1979). Finally, minimum resolvable can be defined as the ability to determine the presence of or ability to distinguish between more than one indentifying feature in a visible target (Kniestedt & Stamper, 2003). The aforementioned author suggests that from a physiologic point of view, minimum resolvable is the detection of brightness differences between adjoining areas and, therefore, depends on object contrast

and the packing density of photoreceptors in the fovea. In a person with a healthy visual system, the threshold of minimum resolvable is between 30 seconds and 1 minute of arc. Although minimum detectable and minimum separable vision can be tested, minimum recognizable resolution is more commonly measured. This is the type of acuity typically taken in a clinical setting with the use of an optotype letter acuity chart.

2.2.2 Development Of Visual Acuity

Salomao, Ejzenbaum, Berezovsky, Saca, & Pereira (2008) reported that sweep VEP grating acuity improves from 0.8 logMAR (20/125 Snellen equivalent) in the first month of life to 0.06 logMAR (20/20 Snellen equivalent) at 36 months of age. Pan, Tarczy-Hornoch, Cotter, Wen, Borchert, Azen, & Varma (2009) reported VA norms for children 30 to 72 months (2.5 to 6 years) of age using the HOTV chart. These authors found that VA improved from 0.32 to 0.02 logMAR during this period. This result differs from another study by Drover, Felius, Cheng, Morale, Wyatt, & Birch (2008) who found that VA improved from 0.08 logMAR at age 3 to -0.06 logMAR at 12 years. A similar result was reported by Dobson, Clifford-Dobson, Green, Miller, & Harvey (2009). These authors found that VA improved from 0.16 at 5 years to -0.02 logMAR at 13 years.

2.2.3 Measurement Of Visual Acuity

VA is the most common primary measure of visual function in both clinical and research settings (Kaiser, 2009; Williams, Moutray, & Jackson, 2008). The clinical standard of "normal vision" (20/20 or 6/6) is the recognition of letters subtending at least 5 minutes of arc with each line and space on an optotype subtending 1 minute of arc (Adler, 1987; Cassin, 1995). In other words, when evaluating VA, the tester is attempting to detect the minimum width of the stroke expressed in minutes of arc that allows the correct identification of the test (absolute threshold).

VA threshold is identified by having a patient read progressively smaller high contrast black letters on a very white background at a prescribed distance. Most authors use the correct identification of 50%+1 of the characters of a defined line on a Snellen chart as the end point (Kniestedt & Stamper, 2003). Testing is done monocularly with one eye occluded, although VA can be tested binocularly when appropriate (i.e. for patients with nystagmus). VA is most often recorded as a fraction, comparing what should be seen at the testing distance to what is seen, measured by standard clinical tests and distances. In this format, the numerator is the distance (in feet or meters) at which the patient is tested, usually 20 feet. The denominator is the distance (in feet or meters) at which the test object subtends an angle of 5 minutes of arc on the retina. Therefore, on a 20/20 line (6/6 in meters), the letter subtends an angle of 5 minutes of arc when viewed at 20 feet (6 meters) (Kniestedt & Stamper, 2003). This is the most widely used notation format in all English speaking countries. Other forms of notation include minimum angle of resolution (MAR), log of the minimum angle of resolution (logMAR), and decimal (Table 1) (Kniestedt & Stamper, 2003). MAR is the angular size of the critical detail that must be resolved for the patients to be able to identify the optotypes correctly (Kaiser, 2009). It can be calculated as the reciprocal of the Snellen fraction. For example, a 6/30 letter would have a MAR of 5 minutes (MAR = 30/6 = 5 minutes). The MAR can also be given in log10 form. This is referred to as logMAR (Kaiser, 2009). In Japan and many European countries, VA is expressed as a decimal that is equal to the numeric value of the Snellen fraction or the reciprocal of the visual angle in minutes (Kaiser, 2009) (Table 1).

Table 1. *Equivalent visual acuity measurements. Snellen VA in meters and feet, decimal notation, MAR (minimum angle of resolution), and LogMAR (logarithm of the minimum angle of resolution)*.

Snellen visual acuity					
20 ft	6 m	4 m	Decimal	MAR	LogMAR
20/640	6/192	4/128	0.03	32	1.5
20/500	6/152	4/100	0.04	25	1.4
20/400	6/120	4/80	0.05	20	1.3
20/320	6/96	4/63	0.063	16	1.2
20/250	6/76	4/50	0.08	12.5	1.1
20/200	6/60	4/40	0.1	10.0	1.0
20/160	6/48	4/32	0.125	8.0	0.9
20/125	6/38	4/25	0.16	6.3	0.8
20/100	6/30	4/20	0.2	5.0	0.7
20/80	6/24	4/16	0.25	4.0	0.6
20/63	6/19	4/12.6	0.32	3.2	0.5
20/50	6/15	4/10	0.4	2.5	0.4
20/40	6/12	4/8	0.5	2.0	0.3
20/32	6/9.6	4/6.4	0.63	1.6	0.2
20/25	9/7.5	4/5	0.8	1.25	0.1
20/20	6/6	4/4	1.0	1.0	0.0
20/16	6/4.8	4/3.2	1.25	0.8	-0.1
20/12.5	6/3.75	4/2.5	1.60	0.63	-0.2

20/10	6/2.8	4/2	2.0	0.5	-0.3

There are numerous VA charts commercially available, but the most common charts used in North America are the Snellen and ETDRS charts (Kaiser, 2009). The Snellen chart, created and first introduced by ophthalmologist Dr. Hermann Snellen in 1862, is the most widely used VA chart in clinical practice. In spite of its wide usage, the Snellen chart has numerous limitations (Kaiser, 2009; Ricci et al., 1998). Consequently, in 1976, two researchers, Drs Ian Bailey and Jan Lovie created a new test called the Bailey-Lovie chart in an attempt to correct the design flaws inherent in the Snellen chart. In 1982, this chart was modified based on the recommendations of the United States (US) Committee on Vision of the National Academy of Sciences, National Research Council, and Working Group 39, and by Dr Rick Ferris for use in the Early Treatment Diabetic Retinopathy Study (ETDRS) (Figure 1) (Early Treatment Diabetic Retinopathy Study (ETDRS) Research Group, 1985; Kaiser, 2009; Lovie-Kitchin, 1988).

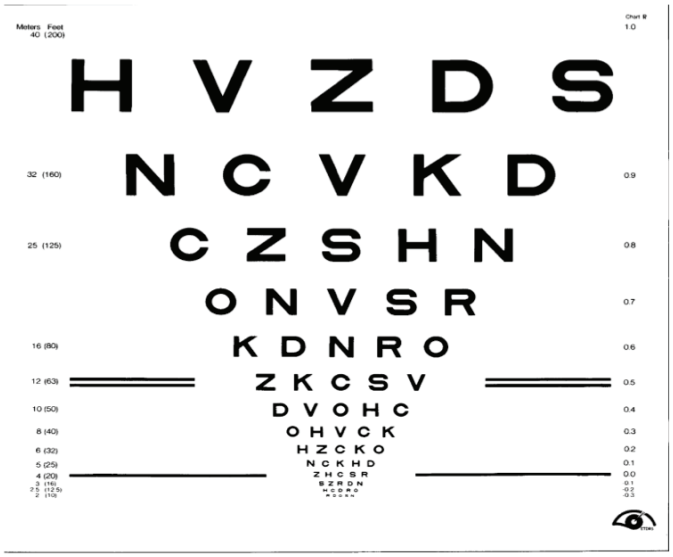


Figure 1. One of three ETDRS charts. Testing of visual acuity is done at 4 meters (Early Treatment Diabetic Retinopathy Study (ETDRS) Research Group, 1985).

The ETDRS visual acuity chart is now considered the "gold standard" for visual acuity assessment. This is because the test incorporates specific design criteria to make it more accurate than the Snellen or Sloan acuity tests (Cotter et al., 2003; Kaiser, 2009; Rosser, Murdoch, Fitzke, & Laidlaw, 2003). These include the same number of letters per row (five letters per row), equal spacing of the rows on a log scale (the rows are separated by 0.1. log unit), equal spacing of the letters on a log scale (to control contour interaction/crowding), and individual rows balanced for letter difficulty (Table 2) (Early Treatment Diabetic Retinopathy Study (ETDRS) Research Group, 1985; Ferris, Kassoff, Bresnick, & Bailey, 1982; Lovie-Kitchin, 1988).

Table 2. *Difficulty scores for each Sloan letter combination in ETDRS charts 1 and 2* (Ferris et al., 1982).

Chart 1	Difficulty score	Chart 2	Difficulty score
NCKZO	410.1	DSRKN	410.1
RHSDK	407.8	CKZOH	407.8
DOVHR	410.7	ONRKD	410.5
CZRHS	411.6	KZUDC	411.6
ONHRC	409.6	VSHZO	409.5
DKSNV	408.4	HDKZR	408.6
ZSOKN	409.3	CSRHN	409.2
CKDNR	410.9	SVZDK	410.8
SRZKD	412.5	NCVOZ	412.6
HZOVC	410.3	RHSDV	410.3
NVDOK	408.8	SNROH	408.8
VHCNO	407.9	ODHKR	408.2
SVHCZ	409.9	ZKCSN	409.7
OZDVK	411.2	CRHDV	411.1

The ETDRS chart has five letters per row ranging in size from +1.0 to -0.3 LogMAR in 0.1 LogMAR steps (Rosser et al., 2003). The ETDRS testing procedure requires that the patient read down the chart starting with the first letter on the top line. The testing continues with a forced-choice paradigm from the top of the chart to the

bottom until the patient makes a complete line of errors or has read all letters on the chart. Patients are required to identify each letter and are encouraged to guess if they are unsure.

The VA score is calculated using an interpolated method (letter by letter scoring). Consequently, the score is derived from the number of correctly named letters (Rosser et al., 2003). This method takes into account any letters missed or read incorrectly at or near threshold or any additional letters read correctly past the nominal threshold value (Lovie-Kitchin, 1988). Each optotype is assigned a score that is equal to the value of the logarithmic progression (0.1 log unit) per line, divided by the number of optotypes (five) per angular width (therefore, 0.1 log unit/5 optotypes on the line = 0.02 log units) (Ricci et al., 1998). Thus, the ETDRS has a grading scale of 0.02 log units per optotype. For example, with this scoring method, a score of 0.06 would not mean detecting letters of 0.06 logMAR size, but refers to the detection of all letters on the 0.1 line and then 2 letters of the 0.0 size. This amounts to a linear interpretation of the MAR between successive line sizes (Stewart, Hussey, Davies, & Moseley, 2006).

The major advantage of the logMAR chart notation for research purposes is the ability to measure and score visual acuities accurately, which can then be included in statistical analysis (Lovie-Kitchin, 1988). The VA scoring method allows arithmetic procedures, including regression analysis and parametric statistics, to be applied to VA scores (Lovie-Kitchin, 1988; Wild & Hussey, 1985). Ricci et al. (1998) also suggests that the easy progression in steps of 0.1 log units may be useful for detecting subtle changes in VA. LogMAR charts are also being adopted into pediatric and strabismic services because of the need for accurate and reproducible VA measurements. In the case of amblyopia, the equal number of letters per line provides equal contour interaction (crowding phenomenon) and the detection of amblyopia is facilitated (Hussain, Saleh,

Sivaprasad, & Hammond, 2006). Furthermore, the ETDRS charts are considered superior to previous charts such as Snellen because measurements have more consistent precision, regardless of whether the patient had high or low levels of VA (Cotter et al., 2003). The test-retest variability of the ETDRS charts were found to be considerably better than previous charts, such as the Snellen chart, varying from ± 0.09 to 0.18 LogMAR (± 4 to 9 letters), depending on whether the patients had normal acuity or ocular pathology (Table 3) (Arditi & Cagenello, 1993; Manny, Hussein, Gwiazda, & Marsh-Tootle, 2003; Rosser, Laidlaw, & Murdoch, 2001; Rosser et al., 2003; Rosser et al., 2003; Stewart et al., 2006).

Table 3. *Published 95% ranges for TRV.*

Authors	TRV (logMAR)	TRV (Letters)
Arditi and Cagenello (1993)	± 0.09	± 4-5 letters
Rosser et al. (2003)	± 0.11	± 5-6 letters
Stewart et al. (2006)	± 0.13	± 6-7 letters
Manny et al. (2003)	± 0.15	± 8 letters
Rosser et al. (2003)	± 0.18	± 9 letters
Rosser et al. (2001)	± 0.18	± 9 letters

Although ETDRS incorporates specific design criteria to make it more accurate than previous VA tests, both researchers and clinicians have identified a number of problems with the chart. The first issue, noted by Ricci et al. (1998) is the use of only 5 letters per line on the ETDRS chart. This increases the possibility of false recognition due to guessing driven by the forced choice method. Due to this, the National Academy of Sciences - National Research Council (NAS-NRC) recommend an update to the ETDRS

chart. They suggest that there should be ten optotypes of the same type size, divided into two rows of five, rather than the current use of five letters on each line of the same type size (NAS-NRC, 1980). Unfortunately, this change has not been implemented in most clinical practice. Second, refraction on the ETDRS can be time consuming and frustrating. Hussain et al. (2006) suggests that patients frequently become lost because of the crowding phenomenon and must read and re-read to locate the correct letters for fixation. They suggest further refinement of the chart is needed to overcome its impracticalities for refraction (Hussain et al., 2006). Finally, although the ETDRS has good test-retest variability, it has been reported that the sensitivity to detect changes in visual acuity at 0.10 logMAR is poor (Rosser et al., 2003). This means that a 2-line (10 optotype) change in VA is necessary to be considered clinically significant. This is a large difference and consequently, the EDTRS may not be sensitive enough to detect small changes in VA during amblyopia treatment. This is problematic for those patients who appear to have reached a plateau in visual acuity during treatment or who have reached equal VA, discontinued treatment, and subsequently suffered a regression of acuity.

2.3 Contrast Sensitivity

2.3.1 Definition

Spatial contrast is a physical dimension referring to the light–dark transition at a border or an edge of an image that delineates the existence of a pattern or object (Owsley, 2003). Contrast is therefore defined as the ratio of the difference in the luminance of these two adjacent areas to the lower or higher of these luminance values.

Contrast can be expressed in two ways (Owsley, 2003). The first, Michelson contrast, refers to periodic patterns (i.e. sine-wave gratings). These are defined as the luminance of the maximum brightest area minus the luminance of the minimally dimmest

area, divided by their sum. The second way contrast can be expressed is in non-periodic patterns, such as letters on charts. In this form, dark targets are presented on spatially extended white backgrounds where contrast is defined as luminance of the background minus luminance of the letter, divided by the luminance of the background.

The amount of contrast required to identify a target is called the contrast threshold. In clinical research or patient care settings, contrast threshold is usually described as CS, where sensitivity is the reciprocal of threshold (Owsley, 2003). For example, a patient with a low threshold is said to have high sensitivity and vice versa. Contrast threshold and CS are expressed on a logrithmic$_{10}$ scale. Thus, a contrast threshold of 0.01 (1%) would be equivalent to a log contrast threshold of -2, a CS of 100, or a log CS of 2 (Owsley, 2003).

2.3.2 Development Of Contrast Sensitivity

A number of authors have examined the changes in CS with maturation (Adams & Courage, 2002; Beazley, Illingworth, Jahn, & Greer, 1980; Gwiazda, Bauer, Thorn, & Held, 1997). Adams & Courage (2002) reported that from 1 month to maturity, CS improves by 1 to 1.7 log units depending on spatial frequency. More specifically, CS matures by about 0.3 log units every three months during the first year of life, then by about 0.2 log units until four years, and finally by about 0.1 log units every year until it reaches adult levels at age 9 years. A study by Gwiazda et al. (1997) reported a similar result. This is an improvement of about 2 log units from infancy to adulthood. Also, much like Gwiazda et al. (1997), Adams & Courage (2002) reported that CS reached maturity at 8 years. Unlike the aforementioned authors, Beazley et al. (1980) reported that CS only reached maturity later between the ages of 18 and 29 years.

Interestingly, a number of authors found that CS development during infancy to 3

to 4 years is characterized by rapid improvements in the higher spatial frequencies (Adams & Courage, 2002; Beazley et al., 1980; Gwiazda et al., 1997). After 4 years of age, improvement in CS appears to be accounted for by relatively greater improvements at the lower spatial frequencies.

2.3.3 Usefulness Of Contrast Sensitivity

In comparison to VA, which is a measure of the recognition of small, high spatial frequency, high contrast letters, clinical tests of CS examine the performance of the eye at the low contrasts. CS may be more informative than VA because VA expresses sensitivity to fine detail only, whereas the CS expresses sensitivity to coarse, intermediate, and fine detail (Kaufman & Alm, 2003). Typically, a contrast threshold is measured across a range of spatial frequencies so that the minimum level of contrast for seeing a target can be determined (Kelly, Pang, & Klemencic, 2012). Both Kelly et al. (2012) and Owsley (2003) report that the human visual system is composed of a series of neural spatial frequency filters, each of which detects and processes a limited range of frequencies that are further processed and result in a visual percept. Furthermore, most visual percepts in our environment consist of multiple spatial frequencies that when combined, produce a visual image. Consequently, CS testing across a range of spatial frequencies allows a more complete investigation of visual function, allows the clinician to more fully understand the visual deficits a patient is experiencing (even if VA is normal or nearly so), and may help detect a deficit at an earlier stage (Kaufman & Alm, 2003; Woods & Wood, 1995).

Owsley (2003) suggested that the usefulness and benefit of CS testing falls into three categories. The first category consists of those situations in which CS uncovers a hidden loss of vision that was not detectable by VA testing. Many ocular diseases and

conditions including amblyopia, cataract, and optic neuritis secondary to multiple sclerosis can affect CS (Comerford, 1983; Elliott & Hurst, 1990; Owsley, 2003; Regan, Raymond, Ginsburg, & Murray, 1981). Some of the abovementioned visual problems may not initially present with a reduction in VA yet still result in a deficit in CS. As a result, CS may assist the clinician in understanding a patient's complaint of poor vision, especially if VA is normal or near normal. The second benefit of CS testing is that it provides another visual method to monitor the impact of treatment intervention. The final category for use of CS testing is that it provides an insight into the extent of a patient's visual disability and functional performance problems. A number of studies have reported a relationship between CS and mobility, driving, reading, face recognition, and the ability to perform everyday tasks (Owsley & Sloane, 1987; Owsley et al., 1998; Whittaker & Lovie-Kitchen, 1993). Owsley (2003) suggests that these problems would not be predicted nor well understood if visual acuity tests alone were used to assess spatial vision. This author further suggests that CS is a logical choice for monitoring patient outcomes of treatment and rehabilitation interventions. With this said, Owsley (2003) suggests that even though there are benefits to the use of CS testing clinically and in the research setting, there is not enough evidence that CS plays a significant role in diagnosis or screening to justify it's inclusion in a general comprehensive eye exam.

2.3.4 Measurement Of Contrast Sensitivity

CS can be measured in a number of ways. For experimental purposes, CS is frequently determined by generating a sinusoidal pattern electronically on a monitor. These systems can be expensive, difficult to set up and calibrate, and require time-consuming psychometric methods (Woods & Wood, 1995). Consequently, they are unsuited to clinical practice. There are a number of rapid, easy to use, chart-based CS

tests that have been developed for clinical practice. These tests include Arden test gratings, the Vistech system, square wave gratings, Cambridge low-contrast gratings, the Melbourne Edge test, and the Pelli-Robson charts (Elliott, Sanderson, & Conkey, 1990; Owsley, 2003; Woods & Wood, 1995).

The present study utilized the Pelli-Robson chart (Figure 2). This test differs from other CS tests because it uses letter targets rather than sine or square wave gratings. Letters are composed of a complex mixture of oblique, curved, horizontal, and vertical square wave targets formed by a whole range of spatial frequencies (Pelli, Robson, & Wilkins, 1988). CS charts using letters therefore measure a broad band of spatial frequencies, unlike CS tests using square wave gratings that measure CS at specific spatial frequencies. Measurements using letter targets also involve a recognition task (or more exactly an identification task from 26 letters). This requires a greater amount of cortical processing than the more simple detection task of CS tests using gratings. CS charts using letters have the advantage in that they are familiar to both patient and practitioner (Pelli et al., 1988). The psychophysical method of letter identification is also excellent because it is a forced-choice technique and therefore free of patient criterion differences (Pelli et al., 1988). It has been shown that forced choice procedures yield more reliable CS results than tests using criterion dependant measures.

Figure 2. The Pelli-Robson CS chart. This test consists of two charts, each of which has different letter sequences but is otherwise identical (precisionvision.com).

A number of studies have reported the test-retest variability (TRV) of the Pelli-Robson chart in normal adult subjects to be between +/- 0.15 and +/- 0.20 (Elliott et al., 1990; Haymes et al., 2006; Lovie-Kitchin, 2000; Simpson & Regan, 1995). Only one study reported the TRV of the Pelli-Robson chart with amblyopic subjects. McKee et al. (2003) reported poor TRV (Pearson and Spearman correlations of 0.45 and 0.67) in a group of 23 amblyopes. Unfortunately, the use of a correlation to describe TRV was shown to be inappropriate by Bland & Altman (1986) and Bland & Bland (1999). These authors suggested that the correlation coefficient measures linear association rather than agreement and that methods can correlate well yet disagree greatly. These authors also reported that correlation depends on the range of measures being assessed; with wider ranges being assessed often resulting in higher correlations but not as a result of better

agreement between the methods being assessed. They concluded that correlation coefficients could be misleading in research assessing agreement between two methods and suggested an alternative method called the limits of agreement (LoA) technique.

2.3.5 Contrast Sensitivity And Amblyopia

The monocular loss of CS in amblyopia has been well established (Abrahamsson & Sjöstrand, 1988; Bradley & Freeman, 1981; Chatzistefanou et al., 2005; Hess, 1996; Levi & Harwerth, 1980; Moseley, Fielder, Irwin, Jones, & Auld, 1997; Pardhan & Gilchrist, 1992; Rydberg et al., 1997). Abrahamsson & Sjöstrand (1988) suggests that strabismic and anisometropic amblyopia have distinct CS deficits at a particular spatial frequency range. In general, these authors suggest that the CSF from a patient with strabismic amblyopia is affected in the high frequency range, while anisometropic amblyopes have reduced CSF over the whole frequency spectrum. A number of other studies have reported different results than those of the previous authors. Bradley & Freeman (1981) found substantial CS deficits in a group of anisometropic and mixed strabismic/anisometropic amblyopes over a broad range of middle and high spatial frequencies. No low frequency losses were found. Pardhan & Gilchrist (1992) found that subjects with strabismic amblyopia showed reduced CS at all spatial frequencies whereas anisometropic amblyopes reported mostly high spatial frequency losses. Lundh & Lennerstrand (1983) reported strabismic amblyopes had significant high frequency losses with only minor losses in the low and mid spatial frequency ranges. In comparison, these authors found that CS deficits were more pronounced in mixed amblyopia in which all spatial frequencies were affected to the same degree. Finally, Chatzistefanou et al. (2005) found that strabismic, anisometropic, and mixed amblyopes had reduced CS at all spatial frequencies. There are a number of possible reasons for the variety of findings in the

previously mentioned studies. Most of these studies used very small sample sizes. Further, all of the studies used a different method to test CS. These factors may have contributed to the variety of results.

Interestingly, some authors have reported a CS deficit in the non-amblyopic eye of functional amblyopes. Both Chatzistefanou et al. (2005) and Lundh & Lennerstrand (1983) reported subnormal CS in the fellow eye of amblyopes when compared to the results of normal subjects.

A number of studies have also examined the relationship between VA and CS in amblyopia. McKee et al. (2003) found a moderate increase in contrast threshold (exponent =0.30) with increasing amblyopia. These authors suggest that the correlation between CS measured with Pelli-Robson and optotype acuity measured with ETDRS visual acuity chart is moderately strong but accounts for 34% of the variance in the two measures (r=0.61). Theses measures indicate that the deficit in contrast sensitivity near the peak of the contrast sensitivity function is minimal in most human amblyopes. Moseley, Stewart, Fielder, Stephens, & MOTAS cooperative (2006) also found that for relatively poor amblyopic eye logMAR acuities (approx. >0.9), there is evidence of a related loss of CS. With that said, when the VA deficit is less severe (approx. <0.9 logMAR) there is little evidence of any relation to log CS. These authors also reported that log CS was weakly though significantly correlated with logMAR acuity for all VA's better than 0.9 (r= -0.19, 95% CI: -0.28 to -0.10) whereas for all VA's of 0.9 or poorer, log CS was markedly and significantly correlated with VA (r=-0.72, 95% CI: -0.83 to -0.53). Rydberg et al. (1997) also reported a significant correlation between Snellen VA and CS tested with the Pelli-Robson chart in a group of adult strabismic and mixed amblyopes (r=0.587, p<0.01).

The effect of amblyopia treatment on CS has been investigated by a number of authors. Chatzistefanou et al. (2005) found that occlusion treatment improved the CS results of the amblyopic and non-amblyopic eyes significantly yet neither eye reached levels achieved by normal controls even when VA reached normal levels. Lundh & Lennerstrand (1983) also reported improvement in CS in strabismic and mixed amblyopes after treatment with the Cambridge stimulation technique, although these improvements only occurred in the high spatial frequencies. Unlike the previous authors, Moseley et al. (1997) found that CS did not improve with occlusion while VA did. With this said, these authors only patched their subjects 1 hour per day and only for one month. In contrast, Lennerstrand & Lundh (1980) reported an improvement in CS after amblyopia treatment, without an improvement in VA. Finally, Moseley et al. (2006) found that CS improved with treatment in a manner that was positively correlated with improvements in VA.

2.4 Hyperacuity

2.4.1 Definition

The term "Hyperacuity", first coined in 1975 by Westheimer refers to sensory abilities in which the whole organism's performance transcends the grain imposed by the anatomical structure and physiological organization of the sensory apparatus (Westheimer, 2009). In the fovea, the diameter of the photoreceptors is in the range of 30 to 60 seconds of arc. A number of authors have reported thresholds for hyperacuity tasks as accurate to 3-6 seconds of arc or better (Buckingham, Watkins, Bansal, & Bamford, 1991; Gwiazda, Bauer, & Held, 1989; von Norden & Campos, 2002; Westheimer, 2009; Westheimer, 1975; Westheimer, 1979). This means that humans can resolve detail with

an accuracy of better than one fifth of the size of the most sensitive photoreceptor (Edelman & Weiss, 1995).

Hyperacuity tasks require a person to identify the location of a feature relative to a reference, the exact nature of whose retinal image is not at issue (Westheimer, 2009). The detection of the stimulus involves the assignment of a local sign to each element of the hyperacuity configuration (Enoch et al., 1999; Lakshminarayanan & Enoch, 1995). Once the stimulus has been detected and a local sign has been assigned to local elements of the stimulus, the process of relative localization is likely accomplished by higher order elements. Comparatively, VA refers to the ability to detect feature components as separate, requiring differentiable retinal image components such as separable peaks and troughs. It has been postulated that the mechanisms underlying hyperacuity may have the general task of form and shape analysis (von Noorden & Campos, 2002).

The perception of hyperacuity is thought to occur by the reconstruction of the visual image in the latter stages of visual processing in the visual cortex (area V1) (Skoczenski & Norcia, 2002; Skoczenski & Good, 2004). A recent study using functional MRI found that a cortical network including frontal, parietal, occipital, and cerebellar structures appear to be involved in the analysis of briefly presented vernier offsets at both supra-and subthreshold levels (Sheth et al., 2007). Unfortunately, these authors did not identify the location of cortical neurons dedicated to the detection of vernier offsets.

2.4.2 Types Of Hyperacuity

There are 3 classic types of hyperacuity. These include vernier, chevron, and bisection (Edelman & Weiss, 1995) (Figure 3). The task in each of these involves reporting the sense of the direction or spatial offset of some parts of the stimulus with respect to the others (Cuiffreda et al., 1991; Gwiazda et al., 1989; Lampert et al., 2002;

Westheimer, 2009; Westheimer, 1975; Westheimer, 1979). Specifically, vernier acuity involves the detection of the misalignment in the direction orthogonal to the line joining two features (Westheimer, 2009). In comparison, bisection involves the discrimination of the separation of two or more features. Finally, a chevron task involves determining if a central line is offset left or right when between two other lines (Edelman & Weiss, 1995).

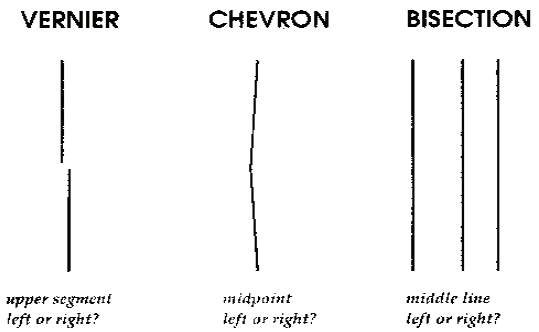


Figure 3. Three classic types of hyperacuity including vernier, chevron and bisection (Edelman & Weiss, 1995).

Other forms of hyperacuity have been identified including oscillatory movement displacement thresholds (OMDT), stereoacuity, positional acuity, and radial deformation acuity (RDA) (Buckingham et al., 1991; Enoch, Werner, Haegerstrom-Portnoy, Lakshminarayanan, & Rynders, 1999; McKee, Welch, Taylor, & Bowne, 1990; Wilkinson, Wilson, & Habak, 1998).

Numerous authors have suggested that hyperacuity would be a useful addition in the clinical assessment of age related changes in the eye, cataracts, and amblyopia. Hyperacuities differ from many other measures of visual performance in that they do not appear to be limited by the optical imperfections inherent in the human eye (Whitaker & Buckingham, 1987). This is because hyperacuities do not depend on resolution but upon stimulus localization. Furthermore, the neural basis of hyperacuity tasks in combination

with the insensitivity of some hyperacuity tasks to optical degradation makes them useful for assessing vision behind ocular opacities as well as for isolating sensorineural factors in visual aging from those attributable to age related change in the ocular media (Kline et al., 2001). Various authors have reported hyperacuity deficits in amblyopic patients (Agrawal, Conner, Odom, Schwartz, & Mendola, 2006; Birch & Swanson, 2000; Bradley & Freeman, 1985; Carkeet et al., 1997; Cox et al., 1996; Drover et al., 2010; Freeman & Bradley, 1980; Harvey et al., 2007; Levi et al., 1997; Levi & Klein, 1982b; McKee et al., 2003; Simmers et al., 1999). Furthermore, Hess (2001) and Hess et al. (1999) suggest that the dominant feature of the perceptual deficit in amblyopia is positional uncertainty (hyperacuity). All of the aforementioned research suggests that hyperacuity has the potential to be a useful addition in the assessment of a number of ophthalmic diseases in a clinical setting. Previous research has suggested that vernier acuity was highly correlated with VA and that the loss of the former could be predicted from the latter. Due to this, vernier acuity has not been adopted in the clinical evaluation of amblyopia. RDA is another form of hyperacuity that research suggests is severely reduced in amblyopia and thus may have the potential to aid in the diagnosis and treatment of amblyopia (Hess, 1999).

2.4.3 Radial Deformation Acuity

RDA can be defined as the ability to detect subtle distortions of a circular D4 (4th derivative of Gaussian contour) shape (Figure 4). Humans with normal vision have a highly acute ability to judge the shape of an object, and to identify and localize distortions in shapes of smooth objects (Wilkinson et al., 1998). RDA, like other hyperacuity tasks, is not affected by contrast reduction and is relatively unaffected by normal aging (Wang, 2001; Wilkinson et al., 1998).

The detection of radial deformation in circles is a shape discrimination task that is thought to be governed by a global pooling mechanism that combines orientation and positional information across space (Hess et al., 1999; Hess, Wang, & Dakin, 1999; Wang, Wilson, Locke, & Edwards, 2002; Wilkinson et al., 1998). Global pooling models are based on input from V1 neurons that provide essential information passed to second stage global pooling mechanisms (Hess et al., 1999). An fMRI study by Wilkinson et al. (2000) found that cells in ventral extra-striate stream (area V4) respond strongly to concentric and radial patterns as well as faces, suggesting that global pooling for shape discrimination might occur there.

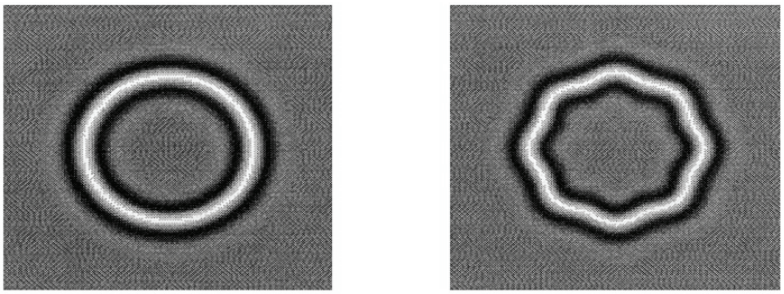


Figure 4. Example of radial deformation stimuli. (a) Circular D4 contour (b) Deformation with radial frequency = 8 cycles per 2π (Wang, 2001).

2.4.4 Development Of Radial Deformation Acuity

A study by Birch, Swanson, & Wang (2000) found that infant sensitivity to radial deformation develops rapidly from 1.4 log unit poorer than adult levels at 4 months to within 0.5 log units of adult level by 12 months. They also found that maturation of this form of hyperacuity is extremely rapid between 4-6 months of age improving by 0.75 log unit during these 2 months. These authors suggest that this pattern of development mimics the developmental pattern of other forms of hyperacuity. A study by Wang,

Morale, Cousins, & Birch (2009) also found rapid improvement in global hyperacuity during the first 5 years of life, reaching the adult range at 7.5 years. Maturation then slows, reaching mean adult level at 21 years of age. Global hyperacuity then decreases slowly in subjects older than 55 years. In contrast, Subramanian et al. (2012) found radial deformation hyperacuity to reach a mature, stable level at 13 years of age for the 1 degree radius 8 RF pattern, but continued to improve through at least 17 years of age for 1 degree radius 16 RF pattern and 0.5 degree radius 8 RF pattern.

2.4.5 Radial Deformation Acuity And Amblyopia

Unlike VA and CS testing, RDA is a tool that has yet to become commonplace in clinical practice. With this said, a number of studies have suggested that RDA may be a useful clinical test for amblyopia. Birch & Swanson (2000) in their study examining the normal maturation of hyperacuity suggested that adults with strabismic amblyopia show a more profound impairment of hyperacuity than grating acuity. This combined with the tendency for grating acuity to overestimate VA suggests that the RDA protocol may provide a sensitive index for determining abnormalities in spatial vision in cases of infantile esotropia (Birch & Swanson, 2000; Subramanian et al., 2012).

To date, four studies have described either the effect of amblyopia and/or strabismus on RDA (Dallala et al., 2010; Hess et al., 1999; Jeffrey, Wang, & Birch, 2004; Subramanian et al., 2012). All authors reported deficits for the detection of radial deformations in amblyopia. Hess et al. (1999) sought to determine if there was a deficit in strabismic amblyopia for global shape detection. These authors found that strabismic amblyopes exhibited abnormalities for detecting radial deformations and these abnormalities affected low as well as high radial frequencies to about the same degree (ie. scale invariance). These deficits were independent of spatial frequency characteristics and

contrast of the stimulus. Jeffrey et al. (2004), in their study assessing the effect of deprivation amblyopia on global shape discrimination also noted scale invariance but suggested that when tested over a larger range of circular contour frequencies, the deficits in radial deformation threshold were not constant. Both Jeffrey et al. (2004) and Hess et al. (1999) found that at suprathreshold levels, the performance of the amblyopic and fellow dominant eye were comparable.

Jeffrey et al. (2004) attempted to assess the effect of deprivation amblyopia on global shape discrimination in patients treated for congenital or developmental cataracts by assessing radial deformation thresholds to circular patterns as a function of circular contour frequency. Circular contour frequency can be defined as the number of radial cycles per degree of unmodulated contour length measured in degrees of viewing angle (Jeffrey, Wang, & Birch, 2002). These authors suggested that this provides a means of evaluating the effect of changes in the neuronal sampling limit on the global pooling process. Jeffrey et al. (2004) found that radial deformation thresholds were elevated in subjects with both unilateral and bilateral deprivation amblyopia and the extent of the deficit was dependent on both the depth of amblyopia and circular contour frequency. Dallala et al. (2010) sought to determine if the deficit in strabismic amblyopia for radial frequency patterns depended on circular contour frequency as Jeffrey et al. (2004) had found in subjects with deprivation amblyopia. Similar to the results of the study by Jeffrey et al. (2004), Dallala et al. (2010) found that the extent of the radial frequency threshold deficit in strabismic amblyopes was dependant on circular contour frequency. With this said, Dallala et al. (2010) suggested that the magnitude of the deficit was smaller in strabismic amblyopia and appeared to be less dependant on circular contour

frequency. With this said, the range of circular contour frequencies investigated were not as extensive as in the study by Jeffrey et al. (2004).

Both Hess et al. (1999) and Jeffrey et al. (2004) attempted to determine whether neural undersampling or neural disarray models could predict changes in radial deformation thresholds. These models are two theories that have been proposed to account for the spatial vision losses in strabismic amblyopia (Wilson, 1991). The neural undersampling model suggests that there is a reduction in the number of thalamic-cortical afferents and/or neuronal cells in V1 (Wilson, 1991). Comparatively, the neural disarray model suggests that there is topographical disarray in the positions of the cortical receptive fields (Wilson, 1991). Hess et al. (1999) reported that both of the aforementioned hypotheses might play a role in strabismic amblyopia. These authors suggested that the current notion of undersampling, unless it is extended to be of a scale invariant nature, cannot be limiting performance in the lower spatial frequency range relevant to the processing of everyday images and in particular the radially modulated D4 stimuli used in the study. In comparison, Jeffrey et al. (2004) attempted to determine which hypothesis might play a role in deprivation amblyopia. They suggested that both neural undersampling and neural disarray might play a role in deprivation amblyopia. They found that elevations in radial deformation threshold were dependant on circular contour frequency, with little or no elevation in threshold at the lowest circular contour frequencies. They suggested that this result was consistent with undersampling at higher radial frequencies. Conversely, results from their second experiment were consistent with elevated "intrinsic noise" above which thresholds from deprived and non-deprived eyes were equal. Jeffrey et al. (2004) suggested that this result was consistent with neural disarray. These authors further suggested that the loss of neural connections from the

ocular dominance columns could occur unevenly with the result that neural sampling varies across the retinotopic map. The resulting patches of sparse arrays with different sampling densities in turn may resemble a jittered array.

Dallala et al. (2010) also sought to determine whether the deficit for the detection of radial frequency patterns in adults with strabismic amblyopia was the result of deficient processing of orientation or position. These authors suggested that the amblyopic deficit for detecting radial frequency patterns was due to anomalous processing of both position and orientation, with a significantly greater deficit occurring for orientation processing (Dallala et al., 2010).

A study by Subramanian et al. (2012) attempted to determine whether RDA could be used as a clinical tool to detect and monitor strabismic amblyopia in young children with the long-term goal of creating a preferential looking test for infants and preschool children. These authors first attempted to determine the sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) for three radial frequency (RF) patterns (0.5 degree radius 8 RF, 1 degree 16 RF, and 1 degree 8 RF patterns). They found that neither of the 1 deg radius patterns (RF 8 and RF 16) had high sensitivity or PPV for strabismic amblyopia, although both had good specificity and moderate NPV. In comparison, the 0.5 deg 8 RF pattern had 83% sensitivity, 85% specificity and 71% PPV. These authors also found that grating acuity had low sensitivity of 38% (95% CI: 15-68%) and PPV=31% (95% CI: 12-58%) and modest specificity of 73% (95% CI: 56-85%) with a NPV of 78% (95% CI: 61-90%).

Subramanian et al. (2012) also sought to examine the relationship between the deficits found with RDA and optotype VA testing. They found significant correlations between two crowded hyperacuity stimuli and optotype acuity among amblyopic

participants (1 deg radius 16 RF stimuli: Spearman r = 0.59, p = 0.013; 0.5 deg radius 8 RF stimuli: Spearman r = 0.83, p = 0.001) and among all participants (1 deg radius 16 RF stimuli: Spearman r = 0.53, p < 0.001; 0.5 deg radius 8 RF stimuli: Spearman r = 0.72, p < 0.001). Furthermore, these authors found that the loss of hyperacuity for 0.5 deg 8RF patterns was proportional to or greater than loss of optotype acuity in strabismic amblyopia.

2.4.6 Critique Of Radial Deformation Acuity And Amblyopia Literature

All of the four articles related to RDA and amblyopia were limited by small sample sizes that reduced their external validity. Jeffrey et al. (2004) suggested that further studies would need a larger number of participants and greater range of amblyopes before firm conclusions could be made concerning the results of their study.

Three of the four studies utilized a control group although none used age-matched controls. This design flaw resulted in bias due to separate sampling of the amblyopes and controls. It should also be noted that Dallala et al. (2010) included one of the authors as part of the control group. This further biases the results of the study.

The participants used in the available research studies were supposed to have either strabismic (Dallala et al., 2010; Hess et al., 1999; Subramanian et al., 2012) or deprivation amblyopia (Jeffrey et al., 2004). Hess et al. (1999) and Dallala et al. (2010) used strabismic and mixed (anisometropia and strabismic) amblyopes in their study. Considering that the purpose of the study was to determine if there were deficits in global processing secondary to strabismic amblyopia, the use of both types of amblyopia makes it difficult to determine whether the deficits were due to the strabismic amblyopia, anisometropic amblyopia or mixed amblyopia. It should also be noted that three of the nine participants in the Dallala et al. (2010) study were reported as having an esotropia or

exotropia of 1 diopter. This is an extremely small size strabismus that is rarely seen clinically. This leads one to wonder if the measurements were accurate. It is more likely that these patients were orthophoric, and thus probable anisometropic amblyopes. Thus, they should have been excluded from the study.

Both Jeffrey et al. (2004) and Hess et al. (1999) attempted to determine which of the theories; neural undersampling or neural disarray could explain the spatial vision losses in strabismic amblyopia. It is interesting that Jeffrey et al. (2004) would attempt to answer this question given that they used participants with deprivation amblyopia secondary to congenital cataracts not strabismic patients. These authors did not specifically note if all of the patients had strabismus. They did note in a table outlining the clinical details of the patients that some did have a history of strabismus surgery. Because of this discrepancy, it is difficult to know if their conclusions regarding the aforementioned theories are correct.

Jeffrey et al. (2004) utilized the HOTV chart with single surround optotypes to test VA. This was a curious choice given that this chart is generally used for young children who are just learning their alphabet. The age range in the aforementioned study was 6 to 30 years of age. Comparatively, Dallala et al. (2010) and Hess et al. (1999) did not identify which VA chart was used in their study.

Both Dallala et al. (2010) and Hess et al. (1999) did not note whether the patients were wearing their most recent cycloplegic refraction. If they were not then the reported results may not be accurate.

All of the aforementioned studies, with the exception of the study by Subramanian et al. (2012) utilized a spatial 2-alternative forced choice paradigm. This results in a

greater chance that the subject will correctly guess which circle was deformed thus possibly overestimating the RDA threshold.

Finally, the forms of amblyopia used in the reviewed research were restricted to strabismic and deprivational. Due to this, one cannot generalize the results of these studies to other forms of amblyopia. This is important because Subramanian et al. (2012) was attempting to determine if RDA could replace Teller grating acuity cards as a clinical tool for the detection of strabismic amblyopia. A test that could only detect one form of amblyopia would have limited clinical value.

The above-mentioned research suggests that measurement of RDA may be useful in the diagnosis and treatment of amblyopia. Additionally, the Early Treatment Diabetic Retinopathy Study visual acuity chart (ETDRS), which is considered the "gold standard" for visual acuity testing in pediatric ophthalmology, may not be sensitive enough to detect small changes in visual acuity during amblyopia treatment (Rosser et al., 2003). These two factors combined with the limitations in the aforementioned RDA literature suggest that more research is needed to determine how amblyopia affects RDA thresholds, how these thresholds compare to VA measurements, as well as if each type of amblyopia is affected to the same degree.

Chapter III: Methods

The present research was a prospective cross-sectional study designed to examine the relationship between VA, CS and RDA in a group of children with amblyopia.

3.1 Recruitment

3.1.1 Participants

Participants for the present study were recruited through the IWK Health Centre Eye Clinic. All staff orthoptists and ophthalmologists were given a list of the study's inclusion and exclusion criteria and asked to inform the principal investigator (PI) of any potential participants. Posters detailing the inclusion/exclusion criteria were also conveniently posted adjacent to areas where patient charts are collected by orthoptists and ophthalmologists. Poster advertisements were also displayed throughout the IWK Health Centre. Finally, the PI reviewed all orthoptic patient charts daily to identify suitable participants (Note: the PI was a staff member of the Eye Clinic and a member of the team who provides clinical care to the patients). It should be noted that potential participants identified at the Eye Clinic were approached by the individual's orthoptist and, if interested, referred to the PI. The PI only directly approached potential participants at the clinic if he was involved in their care.

Routine orthoptic testing assisted in identifying suitable participants and therefore no additional testing was required during the patient's regularly scheduled exam for the purposes of recruitment. This allowed suitable participants (along with their parent/legal guardian, where applicable) to be informed of the study at the end of their regularly scheduled exam and if interested, participate at this time. Interested persons were introduced to the PI by the examining orthoptist. The PI then gave the patient a written information form detailing the study and its potential harms and benefits. The information

form contained the contact information of the PI. Potential participants were asked to review the information form and call or e-mail if they were interested in participating. Once the participant contacted the PI, arrangements were made to obtain consent and perform testing. If the participants were willing to provide consent and perform testing on the same day they were recruited, the testing was done at that time.

Participants were classified into three groups based on the inclusion and exclusion criteria described below. The three groups consisted of participants with anisometropic, strabismic, and mixed forms of amblyopia respectively.

3.1.2 Inclusion And Exclusion Criteria

Inclusion Criteria- All Groups

All participants must:

- Be 6 to 12 years of age.
- Have a diagnosis of anisometropic, strabismic, or mixed forms of amblyopia.
- Have 2 (10 optotypes) or more lines (or had prior to treatment) of interocular difference of vision between their amblyopic and non-amblyopic on the ETDRS logMAR acuity chart. A 2-line interocular difference in visual acuity is the clinical standard for amblyopia as defined in the preferred practice pattern guidelines of the American Academy of Ophthalmology (American Academy of Ophthalmology Pediatric Ophthalmology and Strabismus Panel, 2007).
- Have a visual acuity ≤6/60.
- Wear prescribed refractive correction.
- Have had a cycloplegic refraction in the last 2 years.
- Have the ability to understand English.

An age range of 6-12 years was chosen for the present study based on the results of a study by Wang et al. (2009). These authors found rapid improvement in global hyperacuity during the first 5 years of life with maturation then slowing, reaching the adult range (95% up limit of adult range) at 7.5 years. Another reason for choosing this age group was to ensure that we had a group of children who were capable of competing the Manchester RDA test. This decision was based on the clinical experience of the PI and supervisors. This test had never been used in children prior to this study.

The inclusion criteria for amblyopia associated with strabismus, anisometropia, or both was based on the inclusion criteria used in previous research by the Pediatric Eye Investigator Group (PEDIG) (2003):

Inclusion Criteria-Anisometropic Amblyopia Group

- Amblyopia in the presence of anisometropia of ≥0.5D of spherical equivalent or ≥1.50D of difference in astigmatism in any meridian, with no measureable heterotropia at distance or near fixation, which persisted after at least 4 weeks of spectacle correction.

Inclusion Criteria-Strabismic Amblyopia Group

- Amblyopia in the presence of either a heterotropia at distance and/or near fixation or a history of strabismus surgery (or botulinum) and in the absence of refractive error meeting the criteria below for mixed amblyopia.

Inclusion Criteria-Mixed Amblyopia Group

- Amblyopia in the presence of either a heterotropia at distance and/or near fixation or a history of strabismus surgery (or botulinum) and anisometropia of ≥1.00D spherical equivalent or ≥1.50D of difference in astigmatism in any meridian, which persisted after 4 weeks of spectacle correction.

Exclusion Criteria-All Groups

- Presence of retinal disease or detachment, glaucoma, aphakia/pseudophakia, corneal opacities, cataracts, manifest or latent nystagmus.
- Presence of systemic disease (i.e. diabetes, thyroid, collagen vascular disease), neurological disease (with the exception of extraocular muscle paresis causing strabismus), Autism, developmental delay, Cerebral Palsy (CP), or Attention Deficit Hyperactivity Disorder (ADHD).
- Lack of consent.

Children with clinical evidence of neurological, incapacitating systemic disease, and/or other ocular disease were excluded in an attempt to limit confounding variables in the results of the study. The inclusion of patients with the aforementioned issues would make it more challenging to determine if the results were due to amblyopia or to a preexisting disease process. Apart from these limitations, no participant was excluded on the basis of culture, sex, religion, or emotional, mental and physical disabilities.

3.1.3 Consent

Ethical approval for the research was obtained from the IWK Health Centre Research Ethics Board (REB). Posters containing information about the study were distributed around the IWK Health Centre and Eye Clinic (Appendix H).

When the participant arrived for testing, he/she was presented with the information and consent forms (Appendix A, B, and E). The PI reviewed the forms with the participant. An authorization form was also reviewed with the parent/legal guardian if the participant was still in the care of their parent/legal guardian and required the assistance of their parent/legal guardian to participate in the research (for example to drive the participant to the study site) or if the participant was unable to provide free and

informed consent. The individual's ability to give free and informed consent was assessed during the consent process by asking the participant to reiterate what has been explained them. Either the PI or the research associate) obtained informed consent. The research did not proceed if there was any protesting to the research by the child. If the child wanted to participate, but required the assistance of their parent/legal guardian (for example to drive them to the study site) and the parent would not give their authorization, the individual was not enrolled in the study.

Any questions or concerns the participant or parent/legal guardian had were addressed prior to signing the consent form. It was made clear that participation was completely voluntary and withdrawal from the study could occur at any point during the testing with no negative outcomes to the patient or their care. Participants who were willing to return for a second testing session were re-consented, as this testing was not included in the original consent.

3.1.4 Potential Risks And Benefits

There were minimal anticipated risks to the participants of this study. None of the orthoptic testing required direct contact with the eye or the use of medications. During the testing, participants may have discovered that they had reduced visual acuity that they were not aware of. If this occurred, they were advised to visit their eye care provider for a thorough examination. The potential for a breach of confidentiality was guarded against by storing files containing personal identifying information either in locked cabinets in a locked office at the Health Centre, or on the Health Centre's secure servers. These records will be kept for five years after publication of the results, as required by the IWK Research Ethics Board. No identifying information was used in any publications or presentations of the study results.

Participants also did not personally benefit by participating in this study. Knowledge gained in this study was expected to improve our understanding of how amblyopia affects RDA. It was also hoped that the Manchester Radial Deformation Acuity test would prove to be a feasible test for use in patients with amblyopia. If so, this may allow clinicians to better identify and treat amblyopia.

3.1.5 Compensation

The PI offered to reimburse the cost of parking at the IWK Health Centre for all parents/legal guardians/care givers of the participants. All parents/legal guardians/care givers of the participants rejected this offer. The PI also intended to pay for fuel mileage for those patients who live outside the Halifax Regional Municipality and were not attending a regularly scheduled eye appointment the same day as participation in the current research. This was never required.

3.1.6 Sample Size

Prior to the initiation of recruitment, a sample size of 50 had been estimated to provide the present study with >90% power to detect a small to moderate correlation (>0.2) between RDA and VA. Since this was the first study to obtain data on RDA deficits in a clinical cohort of amblyopic patients, there were no good prior estimates in the published literature of the distribution of RDA and the precision of the measurements in this population. However, we anticipated that a correlation of 0.2 would be a very conservative estimate; the true value would most likely be higher. However, the aim of this study was to characterize the relationship between VA and RDA, rather than to merely detect its presence. Consequently, recruitment was discontinued at thirty-five participants when a statistically significant, moderate correlation $r(35) = -0.42$, p (2-tailed) < 0.05 was noted between the amblyopic deficit found with the Manchester RDA

charts and ETDRS VA chart. Once this correlation was identified, the author utilized an online sample size calculator (http://www.danielsoper.com/statcalc3/calc.aspx?id=1) to ensure a sample of sufficient size had been recruited. A minimum required sample size of 34 participants was indicated, given the desired probability level of 0.05, the number of predictors in the model (2), the effect size (0.42), and the desired statistical power level of 90%. Therefore, given this result, recruitment was discontinued.

3.1.7 Statistical Analysis

The results of the present study were analyzed using the IBM SPSS predictive analytics software. Analysis of the study's results utilized both univariate and multivariate tests. Data summaries were based on mean, median, standard deviation, and range. The results from each group of amblyopes were analyzed using non-parametric tests (Wilcoxon signed ranks test), as the data was not normally distributed. Statistical significance was assumed at the $P < 0.05$ level. The relationship between RDA and VA deficits was established through regression analyses (scatterplots, Spearman correlation coefficients). Analyses also grouped children by age as a proxy for looking at physical and cognitive development (i.e. maturation of the visual system). The methods of Bland & Altman (1986) were used to assess test-retest variability expressed as 80% confidence limits for agreement for the RDA, ETDRS, and Pelli Robson tests, respectively. The Bland Altman method usually requires 95% limits of agreement and the mean difference of testing session 1 and 2. We chose to use the median difference and 80% CI's because the results in this study were not normally distributed.

3.2 Data Collection

3.2.1 Materials

The following instruments were used in the present study:

1) Distance LogMAR ETDRS VA chart (Precision Vision, USA).
    a. CSV-1000 retro-illuminated cabinet for the ETDRS VA chart. This system allows constant lighting conditions and provides a constant test illumination of 85 cd/m^2 (Precision Vision, USA).
2) Manchester RDA charts (Paul H. Artes, U Manchester).
3) Pelli Robson CS test (Clement Clarke, UK).
4) Opticlude patch (3M, Canada).

3.2.2 Experimental Procedure

All subjects were administered the ETDRS VA chart, Pelli-Robson CS chart, and the Manchester RDA chart by the PI who is an experienced, certified orthoptist. All testing was done in the same room (room 14 of the IWK Eye Clinic) with the same lighting conditions with the exception of the participants 6 and 7 who had their CS tested in the 4th floor Pediatric Vision Science Group lab. The VA and RDA testing was done while seated in the examining lane chair as they normally would for their orthoptic appointment and standing for the CS testing. Testing was done monocularly for all three tests using an Opticlude patch (3M, Canada) to cover the participant's eye. VA testing was done first, followed by RDA, and then CS. The results of each test were recorded. Breaks during the testing session were allowed as needed. Testing proceeded at a pace dictated by the participant. The amblyopic eye was tested first, followed by the non-amblyopic eye for each of the aforementioned tests. All participants were tested while wearing their current refractive correction.

3.2.3 Visual Acuity Testing And Scoring

The ETDRS chart was placed 4 meters from the patient in a CSV-1000 back-illuminated stand. The ETDRS chart was printed with high contrast lettering on a

translucent white polystyrene panel lit from behind and displayed in a standard light box. The light box was illuminated by two fluorescent lamps with a reusable fenestrated sleeve (diffuser). Chart luminance is recommended to be between 80 and 320 cd/m^2 (Bailey & Lovie, 1976). This was not measured prior to the initiation of the study.

The ETDRS chart has five letters per row ranging in size from +1.0 to -0.3 LogMAR in 0.1 LogMAR steps (Rosser et al., 2003). The ETDRS testing procedure requires that the patient read down the chart starting with the first letter on the top line. The testing continues with a forced-choice paradigm from the top of the chart to the bottom until the patient makes a complete line of errors or has read all letters on the chart. Patients are required to identify each letter and are encouraged to guess if they are unsure. With this said, since the PI was not blind to the participants previous VA results, it was deemed unnecessary to start VA testing at the top line of the ETDRS chart. Instead, testing was started 2 lines above the participant's previous VA result, starting with the middle optotype and proceeded down to the bottom of the chart or until the participant made a complete line of errors. As with the standard method, participants were given verbal positive reinforcement and were encouraged to guess if they were unsure of an optotype.

The VA score was calculated using the interpolated method (letter by letter scoring). This means that the number of correctly named letters determined the VA score. This method takes into account any letters missed or read incorrectly at or near threshold or any additional letters read correctly past the nominal threshold value (Lovie-Kitchin, 1988). Scores were recorded in Snellen format and later changed to LogMAR.

3.2.4 Contrast Sensitivity Testing And Scoring

The Pelli-Robson chart consists of two charts and one scoring pad. Each of the charts has different letter sequences but is otherwise identical. The chart consists of 8 lines of large letters (20/60 optotype), each letter subtending 3 degrees at the patient's eye from 1 meter. On each line there are two groups, each containing 3 letters. The letters in each group have the same contrast and the contrast in each successive group decreases by $1/\sqrt{2}$ (Elliott et al., 1990). The Pelli-Robson chart should be illuminated as uniformly as possible, so that the luminance of the white area is about 85 cd/m^2 (acceptable range is 60 to 120 cd/m^2). This was not measured prior to testing.

Each participant was positioned one meter from the chart and tested monocularly and binocularly. The participants were instructed to read all of the letters from the top of the chart down until they could no longer identify the letters or they incorrectly identified two of the three letters in a triplet. Participants were encouraged to take their time during the test and asked to guess even when they did not think there was a letter present. The patient's log CS was indicated by the faintest triplet in which two of the three letters were identified correctly.

3.2.5 Radial Deformation Acuity Charts Testing And Scoring

RDA Stimuli

The Manchester RDA stimuli are sinusoidal perturbations of contours constructed from 4th derivatives of a Gaussian contour (D4) (Figure 3). The circular D4 (CD4) is created using the following equation (Hess et al., 1999):

$$CD4 = L_m [1 + c (1 - 4r^2 + 4/3(r^4))e^{-r2}]$$

$$r = \frac{\sqrt{(x^2 + y^2)} - R}{\sigma}$$

$$\sigma = \frac{\sqrt{2}}{\pi\omega_p}$$

Where σ is the space constant of D4, ω_p is the D4 peak spatial frequency, R is the radius of the circular D4 contour, c is the contrast and L_m is the mean luminance of the pattern. Wilkinson et al. (1998) suggests that provided $r_o > 4\sigma$, the radial D4 integrates nearly to zero across its width. This results in a pattern that is spatial frequency narrow-banded. The deformation of the base circles are introduced by sinusoidally modulating the radius according to the formula below:

$$R = R_m [1 + A \sin [f_r \arctan (y/x) + \theta]]$$

Where R_m is the mean radius, f_r is the radial frequency, A is the amplitude of the radial deformation and è is the phase modulation where $0< \theta <2\pi$.

The RDA stimuli are presented on a board printed in high resolution (600 dpi) (Figure 5). The D4 circles are printed on a 0.5% reflectance background and therefore reflect 50% of the light incident on it. The mean radius of the circular stimuli was 0.5°. The radial frequency was 8 cyc/360°. The D4 peak spatial frequency was 5 cyc/deg. The contrast of stimuli was 80%.

Testing and Scoring of the RDA charts

The Manchester RDA charts consist of six charts with twenty increasing RDA levels where the amplitude of deformation decreases (Patel, 2005). The amount by which each circle is deformed on each row decreases by an arbitrary amount making it increasingly difficult for the observer to guess which circle is deformed. At each level on

the Manchester RDA chart, the levels of distortion are stated as log RDA. The score is calculated by taking the radial deformation (as calculated above) as a percentage distortion threshold value. RDA is then stated on the charts as a log of the reciprocal of this threshold value.

At each RDA level on the chart there are 5 circles, one of which is deformed. Each of the charts has the deformed circle on each line in a different position but the charts are otherwise identical. It is the task of the subject to correctly identify which circle is deformed on each line of the chart being used. The choice of five circles increases the repeatability of the charts since it decreases the chances of guessing which circle is deformed. Also, using six charts allow for more variation in presentation possibly reducing learning effects (Patel, 2005). With this said, we decided to use three charts per eye rather than the prescribed six due to the youth of our age group. This change was made because clinical experience suggested that six charts were too time-consuming and difficult for this age group, thus resulting in reduced reliability.

The six RDA charts were separated into two groups, 1, 2, and 3 and 4, 5, and 6. These groups were randomly assigned to each eye at each testing session. Each participant was tested monocularly with the test held at 40 cm (+/- 10cm) working distance. A measuring tape was used to ensure proper testing distance each time the participant started a test. Overhead lighting was used to allow constant illumination during testing. The chart was directly illuminated with a 60-watt light bulb fixed to an overhead lamp. The light's position was adjusted to above the chart. The participants were verbally encouraged to guess the answers on each RDA level. They were stopped after three consecutive incorrect responses on each chart. Participants were given another opportunity at levels where they guessed incorrectly. If an improvement could be made

on the three incorrect responses, the participant was allowed to continue further on the chart until the termination rule applied again.

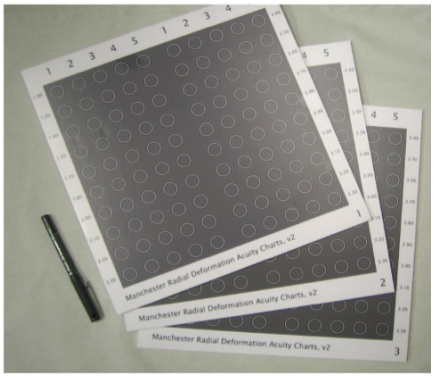


Figure 5. The Manchester RDA charts. Three of six charts are shown here. The charts measure radial deformation acuity. This is the smallest level of radial deformation detected by an observer.

3.2.6 Orthoptic Testing

Other standard orthoptic testing included the assessment of binocular status using Worth4Dot at 1/3rdm and 6m, stereopsis using the Frisby Stereotest, as well as the alternate prism and cover test at 1/3rdm and 6m to determine and quantify the presence or absence of strabismus. The 4 diopter base-in, base-out test was also be used to determine the presence of a central suppression scotoma in those patients whom are suspected to have a microstrabismus.

Chapter IV: Results

Thirty-five participants (18 girls, 17 boys) were recruited from July 2010 and December 2011. Participant ages ranged between 6 and 12.1 years, with a mean of 8.5 years (median=8.3 years, SD=1.7) (Figure 6). Of the 35 participants, 7 were anisometropic, 16 were strabismic, and 12 were mixed amblyopes. Appendix C demonstrates the clinical characteristics of the participants including refractive correction worn, presence or absence of strabismus, binocular status, stereopsis, and current treatment. Ten of the participants (4 girls, 6 boys) agreed to be retested. The mean length of time between testing sessions was 10.9 months (ranging from 9 to 14 months).

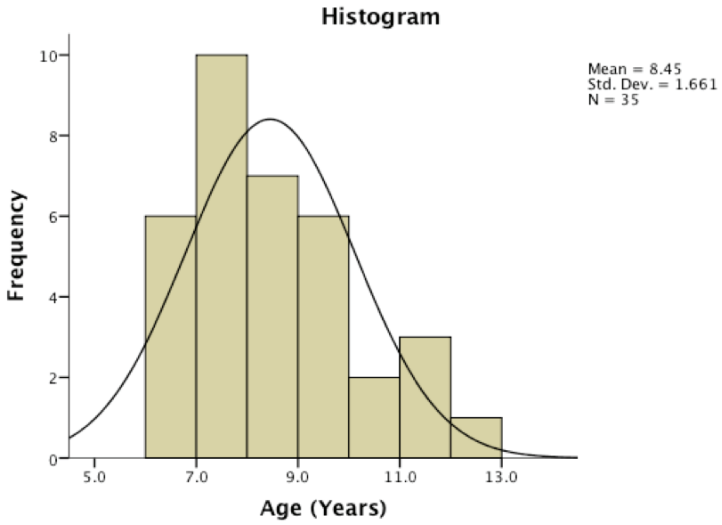


Figure 6. Age frequency of participants.

Amblyopia was treated in this sample of children with occlusion (n=34), atropine penalization (n=2), and Bangeter foil (n=2). Some of the sample required more than one treatment modality. At the time of testing, only one participant was being treated for amblyopia. Of the 35 children, 9 had a history of strabismus surgery. In the group of

children who were retested, only one was treated for amblyopia in the period of time between test sessions.

4.1.1 Normality

Table 4 shows that the median (IQR) deficit was -0.20 (-0.32, -0.12) logMAR for VA, 0.10 (-0.07, 0.23) log for RDA and 0.0 (0.0, 0.0) log for CS. The results of the Shapiro-Wilk normality test for the amblyopic deficit (non-amblyopic eye (NA) – amblyopic eye (A)) determined with VA, RDA and CS tests are also shown in Table 4. This test demonstrates significant non-normality for VA and CS. This result was expected as our sample consisted of amblyopic participants with abnormal VA. These findings support the choice of non-parametric tests used in the analysis of the present study's results.

Table 4. *Mean, standard deviation (SD), median, interquartile range (IQR) for the amblyopic deficit (NA – A) found with VA, RDA and CS tests.*

Test	Mean±SEM	SD	Median	IQR	*P*-value
VA	-0.25±0.36	0.21	-0.20	-0.32, -0.12	0.00
RDA	0.10±0.37	0.22	0.10	-0.07, 0.23	0.06
CS	0.43±0.02	0.13	0.0	0.0, 0.0	0.00

4.1.2 Amblyopic Eye Versus Non-Amblyopic Eye

Appendix D shows the clinical classification of each participant along with their score for the VA, RDA and CS tests. The median and interquartile range for each test is summarized in table 5. A Wilcoxon Signed Ranks test was conducted to compare the

median best corrected VA, RDA, and CS of the amblyopic and non-amblyopic eyes (Table 5). The Wilcoxon Signed Ranks test suggested that there was a statistically significant difference between the underlying distributions of the amblyopic logMAR VA and non-amblyopic logMAR VA, z = -5.071, $p < 0.01$ (computed P=0.00). This was also noted for the distributions of amblyopic eye RDA and non-amblyopic eye RDA, z = -2.556, $p < 0.05$ (computed P = 0.01). There was no significant difference between the median amblyopic and non-amblyopic eye CS, z = -1.781, p = 0.08.

Table 5. *Visual acuity (VA), radial deformation acuity (RDA) and contrast sensitivity (CS) results for the amblyopic (A) and non-amblyopic eyes (NA).*

Chart Type	Eye	Median	Interquartile Range (25%, 75%)	Z-statistic	*P*-value
VA	A	+0.24	+0.12, +0.4	-5.071	0.00
	NA	+0.04	-0.06, +0.12		
RDA	A	2.63	2.53, 2.77	-2.556	0.01
	NA	2.73	2.53, 2.87		
CS	A	1.95	1.8, 1.95	-1.781	0.08
	NA	1.95	1.95, 1.95		

4.1.3 Comparison Of Amblyopic Deficit With RDA, VA, And CS

It was not possible to directly compare the results of RDA, VA, and CS because each of these tests measure a different visual function and each is scored differently. Therefore, a scatterplot was used to compare the magnitude of the amblyopic deficit with

each test (Figure 7, 8 and 9). The amblyopic deficit was defined as the interocular difference for each test.

Figure 7 is a scatterplot comparing the amblyopic deficit with RDA and VA. The RDA interocular difference (y-axis) was determined by subtracting the results for the amblyopic eye from the non-amblyopic eye (NA-A) for each participant. The VA interocular difference (x-axis) was determined by subtracting the non-amblyopic eye results from the amblyopic eye results (A-NA) for each participant. For each axis on figure 7, the larger the positive number on the scale, the greater the amblyopic deficit.

Spearman's rho revealed a statistically significant, moderate relationship between the amblyopic deficit in RDA and VA ($r(35) = -0.42$, p (2-tailed) < 0.05) (Figure 7). The negative correlation was expected because VA and RDA are scored inversely. With respect to VA, a smaller number represents a better result whereas a larger number represents a better result in RDA. Figure 7 demonstrates that in general, if a participant had relatively good VA, they had relatively good RDA. The coefficient of determination was $r^2 = 0.17$ (Figure 7). This means that 17% of the total variation in RDA can be explained by the linear relationship between RDA and VA (as described by the regression equation). The other 83% of the total variation in y remains unexplained. It should be noted that the Spearman rank order correlation differs from the coefficient of determination because the former measures the strength of association between two ranked variables, whereas the latter measures the goodness of fit of a regression. The coefficient of determination is a process in which it is possible to predict future outcomes of a situation on the basis of the given information.

In this sample of participants there were very few children with deep amblyopia. This was an expected finding given the age group from which we recruited. Most children

of this age group who attend the IWK Health Centre Eye Clinic would have already been treated or were in treatment for their amblyopia at the time of recruitment. What can be inferred from the results of figure 7 is that when amblyopia is treated, there does not appear to be a profound deficit in RDA.

Finally, in this sample, 13 participants reported better RDA in their amblyopic eye than in their non-amblyopic eye. This can be contrasted by the VA results where only one participant had slightly better VA in their amblyopic eye than non-amblyopic eye. It should be noted that cooperation in this group was mostly "Good" (n=6) or "Fair" (n=5).

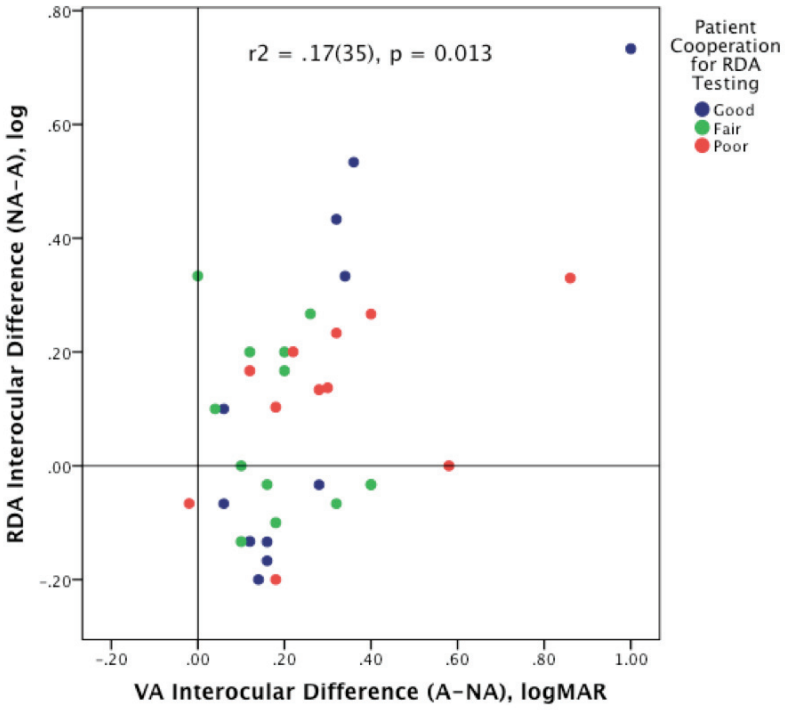


Figure 7. Scatterplot comparing the amblyopic deficit in RDA and VA.

Figure 8 is a scatterplot comparing the amblyopic deficit with RDA and CS. The RDA interocular difference (y-axis) was determined by subtracting the results for the amblyopic eye from the non-amblyopic eye (NA-A) for each participant. The CS interocular difference (x-axis) was also determined by subtracting the amblyopic eye

results from the non-amblyopic eye results for each participant. For each axis on figure 8, the larger the positive number on the scale, the greater the amblyopic deficit. It should be noted that the data plotted on this graph was jittered because most of the participants had no CS interocular deficit resulting in overlapping data points.

Spearman's rho revealed a small relationship between the amblyopic deficit in RDA and CS ($r(35) = 0.27$, p (2-tailed) = 0.117) (Figure 8). The coefficient of determination was $r^2 = 0.07$ (Figure 8). This means that 7% of the total variation in RDA can be explained by the linear relationship between RDA and CS (as described by the regression equation). The other 93% of the total variation in y remains unexplained. This figure demonstrates that in general, even if a participant had good amblyopic eye CS, they could still have a large interocular difference in RDA.

As was stated previously, 13 participants reported better RDA in their amblyopic eye than in their non-amblyopic eye. Only one participant had slightly better CS in their amblyopic eye than non-amblyopic eye.

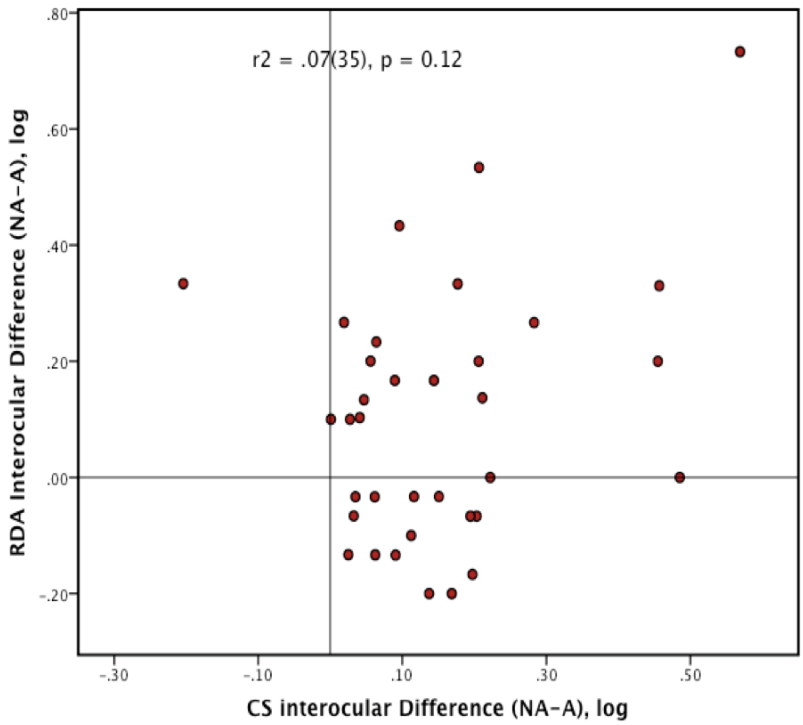


Figure 8. Scatterplot comparing the amblyopic deficit in RDA and CS. The data plotted on this graph was jittered because most of the participants had no in CS interocular deficit resulting in overlapping data points.

Figure 9 is a scatterplot comparing the amblyopic deficit with VA and CS. The VA interocular difference (y-axis) was determined by subtracting the results for the non-amblyopic eye from the amblyopic eye (A-NA) for each participant. The CS interocular difference (x-axis) was also determined by subtracting the amblyopic eye results from the non-amblyopic eye (NA-A) results for each participant. For each axis on figure 9, the larger the positive number on the scale, the greater the amblyopic deficit. It should be noted that the data plotted on this graph was jittered because most of the participants had no CS interocular deficit resulting in overlapping data points.

Spearman's rho also revealed a statistically significant, moderate relationship between the amblyopic deficit in VA and CS ($r(35) = -0.53$, p (2-tailed) < 0.01) (Figure

9). The coefficient of determination was $r^2 = 0.28$ (Figure 9). This means that 28% of the total variation in VA can be explained by the linear relationship between VA and CS (as described by the regression equation). The other 72% of the total variation in y remains unexplained.

As was suggested for the previous figure, most participants had no interocular difference in CS. This is not immediately obvious in figure 9 because the data points have been jittered to avoid overlapping data points. This figure demonstrates that only those participants who had a significant VA deficit were found to have a deficit in CS using the Pelli Robson CS test. The majority of the participants who had four lines or less of interocular difference on VA testing had no CS deficit.

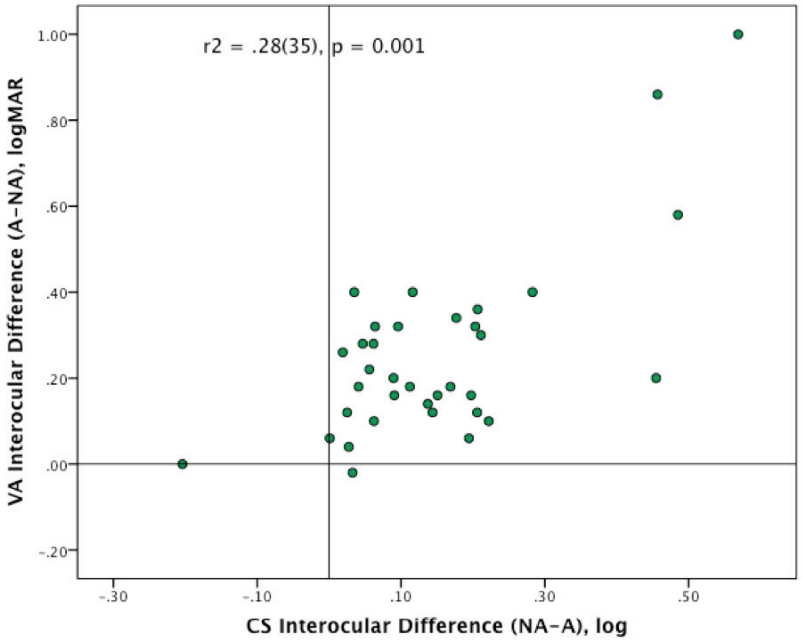


Figure 9. Scatterplot comparing the amblyopic deficit in VA and CS. The data plotted on this graph was jittered because most of the participants had no in CS interocular deficit resulting in overlapping data points.

4.1.4 Gender Effect

The effect of gender was examined first by calculating the median and range (median/range) of the amblyopic deficit in VA, RDA, and CS for each gender (Table 6). This table demonstrates the similarities in the median and range of the boy and girl groups for amblyopic deficit.

A Mann-Whitney test was conducted to determine whether there was any difference in the magnitude of the amblyopic deficit in VA, RDA and CS when participants were separated by gender. The results showed no significant difference between the boys and girls for amblyopic deficit (VA: $U(35) = 138.5$, $z = -0.479$, $p = .63$ / RDA: $U(35) = 117.5$, $z = -1.172$, $p = .24$ / CS: $U(35) = 137$, $z = -0.719$, $p = .47$).

Table 6. *Median and range (median/range) of the amblyopic deficit found with VA, RDA and CS tests. Scores are separated by gender (boys - B, girls – G).*

	Gender	Median	Range	Z-statistic	*P*-value
VA	B	-0.18	0.96	-0.479	0.63
	G	-0.21	0.88		
RDA	B	0.1	0.93	-1.172	0.24
	G	0.167	0.70		
CS	B	0	0.45	-0.719	0.47
	G	0	0.6		

4.1.5 Age Effect

A Spearman correlation was done to determine if there was a relationship between the age of the participants and the results of the VA, RDA and CS tests. The results suggest that there was no relationship was between age and performance for any of the

three tests used in this study (Table 7). Furthermore, there was no relationship between age and size of amblyopic deficit for any of the three tests (Table 8).

Table 7. *Correlation of participant age and performance on the Manchester RDA charts, ETDRS chart, and Pelli-Robson (PR) chart for the amblyopic (A) and non-amblyopic eyes (NA).*

		VA-NA	VA-A	RDA-NA	RDA-A	CS-NA	CS-A
Age	Correlation Coefficient	-0.13	-0.21	0.14	0.04	-0.12	0.19
	Sig. (2-tailed)	0.44	0.22	0.43	0.83	0.49	0.28

Table 8. *Correlation of participant age and amblyopic deficit measured on the Manchester RDA charts, ETDRS chart, and Pelli-Robson (PR) chart.*

		VA Deficit	RDA Deficit	CS Deficit
Age	Correlation Coefficient	0.12	0.06	-0.25
	Sig. (2-tailed)	0.50	0.74	0.15

4.1.6 Cooperation During RDA Testing

Cooperation during RDA testing was rated as "Good", "Fair" or "Poor" (Table 9). Poor cooperation by the participant was defined as frequent random guessing and the participant requiring frequent prompting to look at the chart. Fair cooperation was defined as initial cooperation but the participant appeared to lose focus over the course of testing. These participants eventually required frequent reminders to pay attention to the task.

Finally, good cooperation was defined as good focus and attention throughout testing. These participants were clearly and consistently trying to correctly identify the deformed circles.

Table 9 shows that cooperation during RDA testing was rated as "Good" or "Fair" in 24 of 35 (69%) of participants. All participants completed the test.

Table 9. *Cooperation during RDA testing.*

	Good	Fair	Poor	Total
Anisometropic	2	3	2	7
Strabismic	6	5	5	16
Mixed	3	5	4	12
Total	11	13	11	35

4.1.7 Time To Completion For RDA Testing

The descriptive statistics for the participant's RDA testing duration are listed in Table 10. Testing duration was recorded in 26 participants. The first nine participants were not timed. Time to completion ranged from 5 minutes, 34 seconds to 16 minutes, 3 seconds. The mean time to completion was 10 minutes, 8 seconds (SD = 2 minutes, 24 seconds).

Table 10. *Descriptive statistics for RDA testing duration*

	N	Minimum	Maximum	Mean	SD	Median	IQR
Duration of RDA testing	26	0:05:34	0:16:03	0:10:08	0:02:24	0:09:50	0:08:35, 0:12:05

4.1.8 Test-Retest Variability

The methods of Bland & Altman (1986) were used to assess test-retest variability in 10 participants expressed as 80% confidence limits for agreement for the Manchester RDA, ETDRS, and Pelli Robson tests, respectively (Figures 10 - 16). The results of the analysis are summarized in Table 11. This table shows that there was no median change from session 1 to 2 for all tests with the exception of RDA where a 1 to 2-line improvement was noted. Retest variability for the Manchester RDA charts was 3-4 lines. In comparison, retest variability for VA was 3 letters for the non-amblyopic eye and 18 letters for the amblyopic eye. Finally, retest variability for CS was 1 line for either eye.

Table 11. *Test retest agreement of the Manchester RDA charts, ETDRS chart, and Pelli-Robson (PR) chart for the amblyopic (A) and non-amblyopic eyes (NA).*

	Median Difference		80% CI (90% upper, 10% lower)		TRV (80% confidence limits for agreement)	
	A	NA	A	NA	A	NA
RDA (log)	-0.13	-0.2	0.2, -0.23	0.07, -0.27	0.43	0.34
ETDRS (logMAR)	0	0	0.18, -0.18	0.02, -0.04	0.36	0.06
PR (log)	0	0	0, -0.15	0, -0.15	0.15	0.15

Manchester RDA charts

Figure 10 illustrates the difference between amblyopic eye RDA scores for session 1 and 2 versus the mean amblyopic eye RDA scores for the two sessions. This figure shows a median improvement of -0.13 log (approximately 1 line) from session 1 to 2 represented by the solid line. Figure 10 also demonstrates that two participants had a regression in amblyopic eye RDA from session 1 to 2, one of which was significant. The remaining eight had some improvement. Of the ten participants, nine had a mean RDA result between 2.50 and 3.00 log. Finally, the coefficient of repeatability (or test retest variability –TRV) for the amblyopic eye RDA was 0.43 log. This suggests that a change of ≥0.43 log (or about 4 lines of RDA) would be required to establish a clinically significant change in a participant's RDA.

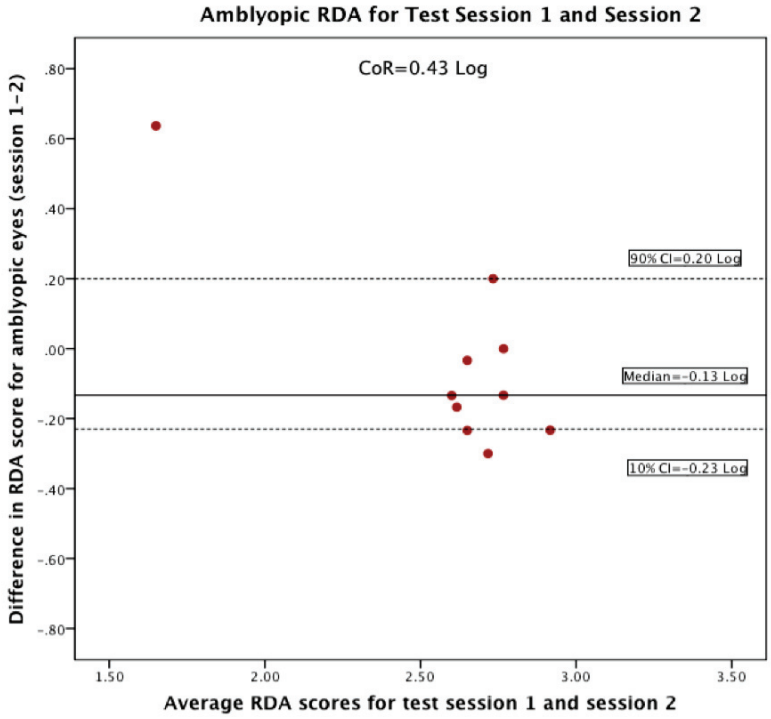


Figure 10. Bland Altman plot of the amblyopic eye RDA results. The y-axis displays the difference in amblyopic eye RDA values for session 1 and 2. The x-axis displays the mean RDA score values for the two test sessions. The dotted lines represent the upper and lower confidence intervals. The solid line is the median difference in log RDA (-0.13 log). All values with a negative number had an improvement in log RDA from session 1 to 2.

Figure 11 illustrates the difference between non-amblyopic eye RDA scores for session 1 and 2 versus the mean non-amblyopic eye RDA scores for the two sessions. This figure shows a median improvement of -0.2 log (2 lines) in non-amblyopic eye RDA from session 1 to 2. Furthermore, eight of the subjects had an improvement in RDA from session 1 to 2. Finally, the coefficient of repeatability for the non-amblyopic eye RDA was 0.34 log. This suggests that a change of ≥0.34 log (or about 3 lines of RDA) would

be required to establish a clinically significant change in a subjects non-amblyopic eye RDA.

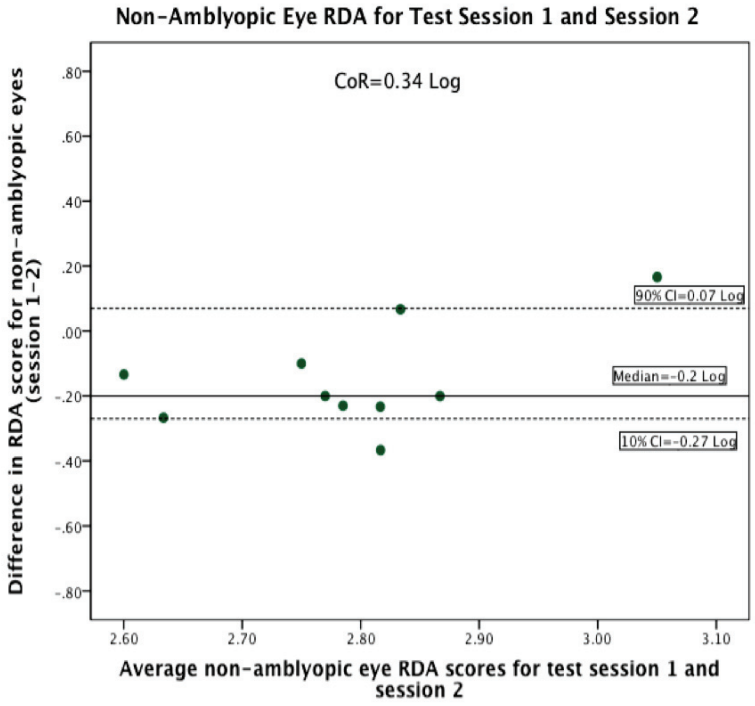


Figure 11. Bland Altman plot of the non-amblyopic eye RDA results. The y-axis displays the difference in non-amblyopic eye RDA values for session 1 and 2. The x-axis displays the mean non-amblyopic eye RDA values for the two test sessions. The dotted lines represent the upper and lower confidence intervals. The solid line is the median difference in log RDA (-0.2 log). All values with a negative number had an improvement in Log RDA from session 1 to 2.

Visual acuity

Figure 12 illustrates the difference between amblyopic eye VA scores for session 1 and 2 versus the mean amblyopic eye VA scores for the two sessions. Figure 12 shows that there was no median change in logMAR VA from session 1 to 2. This figure shows that eight of the ten data points lie within the 80% confidence intervals. Of the ten

participants, nine had mean VA's of 0.4 logMAR or better. Figure 12 also shows that three participants had an improvement in VA, three had no improvement, and four had a small decrease in VA from session 1 to 2. Only one participant in the retested sample had deep amblyopia. Finally, the coefficient of repeatability for the amblyopic eye VA was 0.36 logMAR. This suggests that a change of ≥0.36 logMAR (or about 18 optotypes) would be required to establish a clinically significant change in amblyopic eye VA.

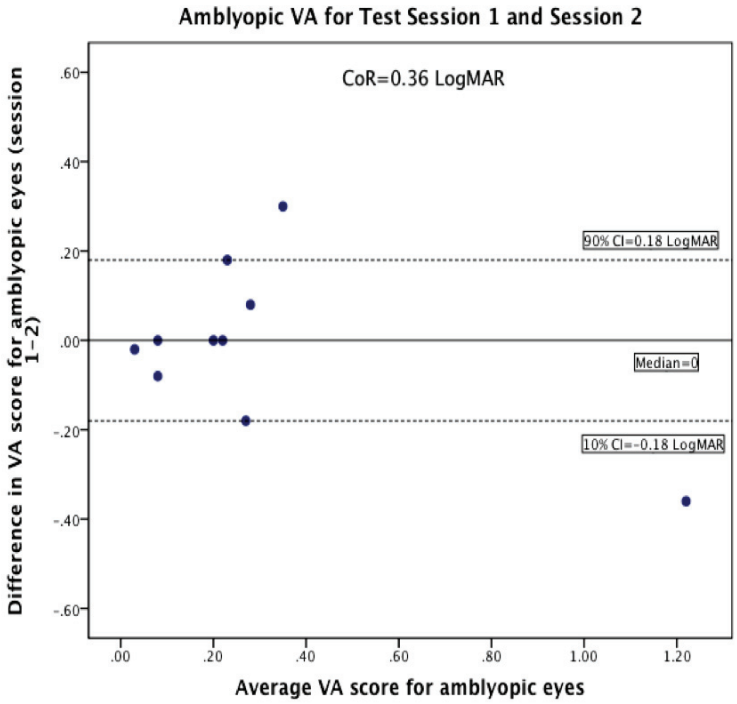


Figure 12. Bland Altman plot of the amblyopic eye VA results. The y-axis displays the difference in amblyopic eye VA values for session 1 and 2. The x-axis displays the mean amblyopic eye VA values for the two test sessions. The dotted lines represent the upper and lower confidence intervals. The solid line is the median difference in logMAR VA (0 logMAR). All values with a positive number had an improvement in logMAR VA from session 1 to 2.

Figure 13 illustrates the difference between non-amblyopic eye VA scores for session 1 and 2 versus the mean non-amblyopic eye VA scores for the two sessions. This figure shows that there was once again, no median change in logMAR values form session 1 to 2. Figure 13 also demonstrates that seven of the ten mean VA's were better than 0.1 logMAR. Of the ten participants, eight had a very minimal change in VA, one had a greater than 2-line improvement, while one had a greater than 2-line decrease in VA. Finally, the coefficient of repeatability for the non-amblyopic eye VA was 0.06 logMAR. This suggests that a change of ≥0.06 LogMAR (or about 3 optotypes) would be required to establish a clinically significant change in non-amblyopic eye VA.

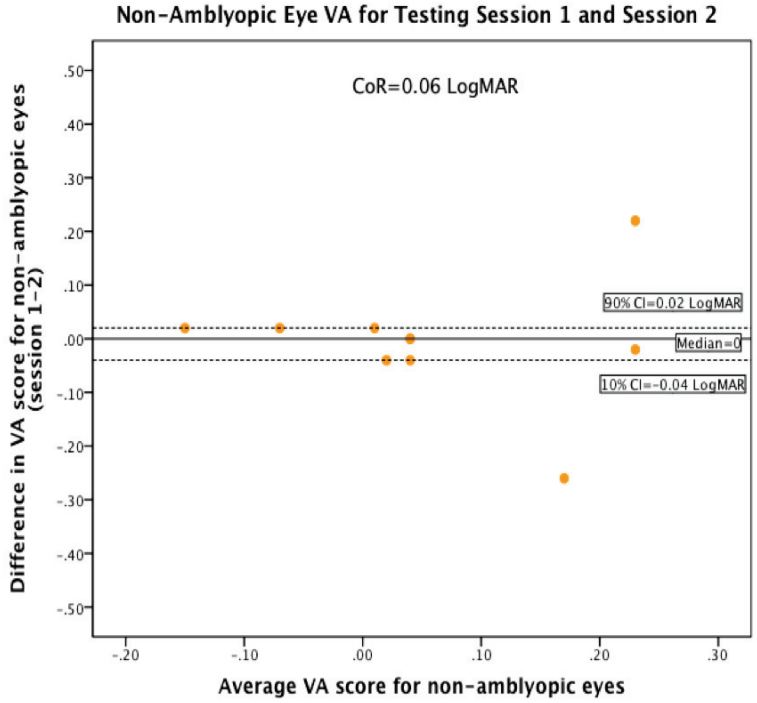


Figure 13. Bland Altman plot of the non-amblyopic eye VA results. The y-axis displays the difference in non-amblyopic eye VA values for session 1 and 2. The x-axis displays the mean non-amblyopic eye VA values for the two test sessions. The dotted lines represent the upper and lower confidence intervals. The solid line is the median difference

in logMAR VA (0 logMAR). All values with a positive number had an improvement in logMAR VA from session 1 to 2.

Contrast sensitivity

Figure 14 illustrates the difference between amblyopic eye CS scores for session 1 and 2 versus the mean amblyopic eye CS scores for the two sessions. The data plotted on this graph was jittered because most of the points overlapped. This figure shows that there was no median change in log CS from session 1 to 2. This figure also reveals that the median and the upper limit of the CI were both zero. Further, all values lie within the 80% confidence intervals. Of the ten participants who were retested, seven had no change in CS while three had an improvement from session 1 to 2. Figure 13 also shows that six subjects had a mean CS of 1.95 log, three had a mean of 1.88 log, while one had a mean of 1.50 log. Finally, the coefficient of repeatability for the amblyopic eye CS was 0.15 log. This suggests that a change of ≥0.15 log (1 line) would be required to establish a clinically significant change in a subject's amblyopic eye CS.

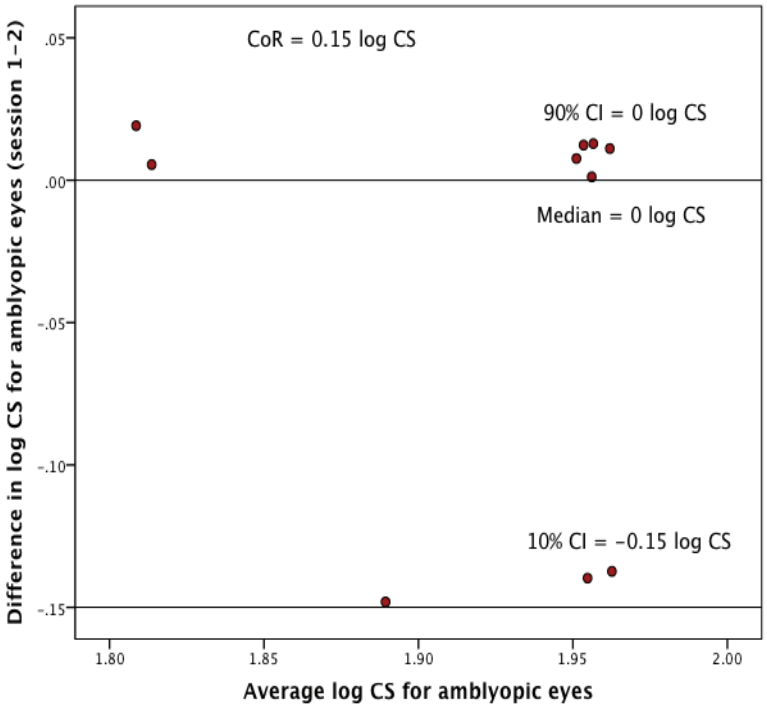


Figure 14. Bland Altman plot of the amblyopic eye CS results. The y-axis displays the difference in amblyopic eye CS values for session 1 and 2. The x-axis displays the mean amblyopic eye CS values for the two test sessions. The dotted lines represent the upper and lower confidence intervals. The solid line is the median difference in log CS (0 log). All values with a negative number had an improvement in log CS from session 1 to 2. The data plotted on this graph was jittered because most of the points overlapped.

Figure 15 illustrates the difference between non-amblyopic eye CS scores for session 1 and 2 versus the mean non-amblyopic eye CS scores for the two sessions. The data plotted on this graph was jittered because most of the points overlapped. This figure shows that there was no median change in Log CS from session 1 to 2. Figure 15 reveals that all but three data points lie within the confidence intervals. Of the ten participants, seven had no change in CS, two had an improvement in CS, and one had a decrease in CS from test session 1 to 2. Further, seven subjects had a mean CS of 1.95, 1 had a mean of

1.88, while two had a mean of 1.80 log. Finally, the coefficient of repeatability for the non-amblyopic eye CS was 0.15 log. This suggests that a change of ≥0.15 log (1 line) would be required to establish a clinically significant change in non-amblyopic eye CS.

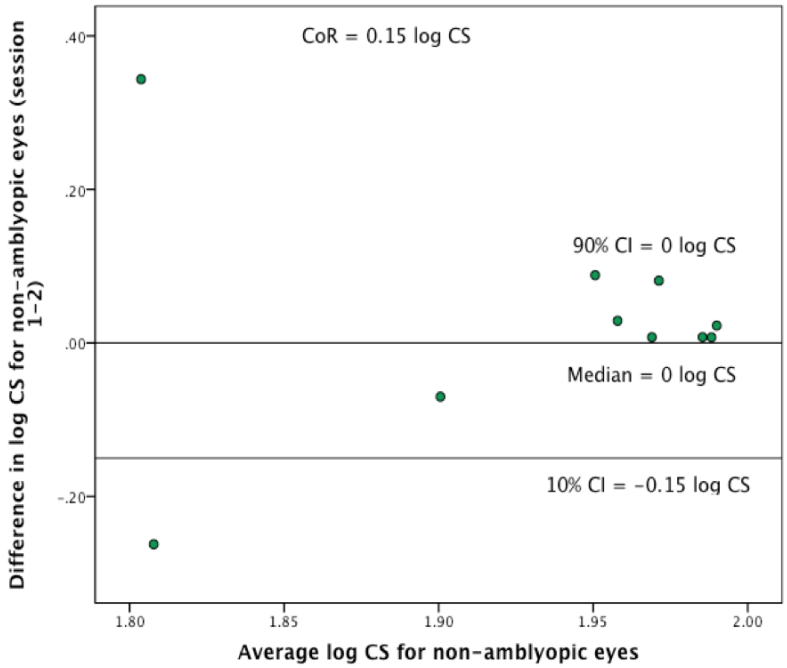


Figure 15. Bland Altman plot of the non-amblyopic eye CS results. The y-axis displays the difference in non-amblyopic eye CS values for session 1 and 2. The x-axis displays the mean non-amblyopic eye CS values for the two test sessions. The dotted lines represent the upper and lower confidence intervals. The solid line is the median difference in log CS (0 log). All values with a negative number had an improvement in log CS from session 1 to 2. The data plotted on this graph was jittered because most of the points overlapped.

Chapter V: Discussion

In this study, the effect of amblyopia on RDA was examined for the first time using the Manchester RDA charts. Of particular interest was the relationship between amblyopic deficits in RDA and VA. Additionally, the TRV of the Manchester RDA charts was assessed.

5.1.1 Comparison Between Radial Deformation Acuity And Visual Acuity In Patients With Amblyopia

The present study found that the median RDA and VA of the amblyopic eye were reduced compared to the non-amblyopic eye (Table 5). This result was not found in CS tested with the Pelli-Robson chart. The identification of an amblyopic deficit in RDA and VA was not surprising as there have been a number of studies that have reported deficits in these visual functions (Abrahamsson & Sjöstrand, 1988; Chandna, Gonzalez-Martin, & Norcia, 2004; Levi, McKee, & Movshon, 2010; McKee et al., 2003; Simmers et al., 1999; Subramanian et al., 2012). What is interesting is that the interocular difference was largest and statistically significant for RDA and VA whereas, CS showed no median interocular difference. Figure 9 clearly demonstrates that only those participants who had a significant VA deficit were found to have a deficit in CS using the Pelli-Robson CS test. The majority of the participants who had four lines or less of interocular difference on VA testing had no CS deficit. A number of other studies have reported a similar result with the Pelli-Robson chart. In a study of 3 to 8 year old children with amblyopia, Moseley et al. (2006) reported that a log CS amblyopic defect was only present in those children with amblyopic eye VA >0.9 logMAR. Where the acuity deficit was less than this, there was little evidence of a loss of CS. Similarly, McKee et al. (2003) reported only a moderate increase in Pelli-Robson CS with increasing amblyopia. These authors noted that even the most severe amblyopes in their sample were only about 3 times worse in CS than average normal observers. Both of the

aforementioned studies suggested that the spatial visual loss in all but the most severe amblyopes occurs in an area of resolution and contrast space towards the high spatial frequency area of the CSF. Unfortunately, this area lies beyond that sampled by the Pelli-Robson chart (1-1.6 cyc/deg). They suggest that it is only where the resolution deficit encroaches into the spatial frequency domain sampled by the Pelli-Robson chart that a CS deficit likely to be noted. As most of the subjects in the present study were either being treated or had been treated for amblyopia at the time of testing, their amblyopic deficit may not have been significant enough to be detected by the Pelli-Robson chart. There are a number of other plausible reasons for our finding. One, it is possible that CS had a more complete recovery from amblyopia because it was not as severely affected as RDA and VA. Simmers et al. (1999) suggested that not all visual functions are affected equally in amblyopia. Furthermore, both Simmers et al. (1999) and Moseley et al. (2006) reported that patching improved all aspects of visual function including CS and suggested that an amblyope could show no improvement in one visual function yet be improving in another. Consequently, it is plausible that CS improved faster and more completely in our sample of amblyopes.

Interestingly, the median Pelli-Robson CS values for both the amblyopic and non-amblyopic eyes shown in Table 5 appear to be better than those found in all reviewed research using the Pelli-Robson chart with the exception of one paper by Moseley et al. (2006). These authors reported a mean amblyopic CS of 1.92 log after treatment with glasses and occlusion. Most of the improvement in CS (0.21 log) appeared to occur after the initiation of refractive correction. Only a minimal improvement in CS was found after occlusion therapy (0.07 log). These authors did not report the changes in the non-amblyopic eye with refractive correction. Unfortunately, it is possible that some of these subjects did not

have amblyopia as the diagnosis appeared to be made prior to the initiation of refractive correction. In contrast, a number of studies using normal subjects reported lower Pelli-Robson CS values then the present study. Leat & Wegmann (2004) found the median CS for their group of 17 normal subjects aged 6 to 8 years to be 1.68 log when tested at 1 meter. These authors further noted that the mean log CS for their adult control group (age 23 to 27 years) was 1.79 log. This was also less than the mean log CS found in our study. Mantyjarvi & Laitinen (2001) had a similar finding in 6 to 9 year old children. They found a mean CS of 1.72 for the RE and 1.76 for the LE. In a group of 10 to 19 year olds, they found a mean CS of 1.73 for the RE and 1.74 for the LE. In comparison, Hargadon, Wood, Twelker, Harvey, & Dobson (2010) reported lower mean contrast sensitivities (1.63 and 1.65 log) in a group of 6-year-old children than the previous authors. Finally, Myers, Gidlewski, Quinn, Miller, & Dobson (1999) reported similar results to the aforementioned authors in a large group of 10 year olds. It is not immediately obvious why the aforementioned results are different than those reported in the present study. It is possible that the Pelli-Robson chart was not properly illuminated in the present study resulting in inflated scores.

The median visual acuities in the present study were similar to other studies of similar age groups. The median VA for the non-amblyopic eye in the present study (0.04 logMAR) aligned well with previously published norms for children aged 6 to 12 years (0.09 to -0.01 logMAR) using the ETDRS VA chart (Dobson, Clifford-Donaldson, Green, Miller, & Harvey, 2009). With respect to the amblyopic eye, a number of studies have reported mean amblyopic and non-amblyopic eye VA for age groups similar to the present study. Hargadon et al. (2010) reported the mean VA for the non-amblyopic and amblyopic eyes (0.04 and 0.57 logMAR respectively) in a group of 6-year-old children. In a large group of 10-year-old subjects, Myers et al (1999) reported mean logMAR VA of -0.09 and -0.04 respectively.

Interestingly, these authors reported better scores for the first eye tested for both VA and CS and thus postulated that fatigue during testing of the second eye may have affected the results. Moseley et al. (2006) reported a mean amblyopic eye VA of 0.42 logMAR. These authors did not report a mean non-amblyopic eye VA after initiation of refractive correction.

As was noted previously, amblyopia resulted in deficits for RDA in most participants (Figure 7). Furthermore, there was a significant difference in the median log RDA results of the amblyopic and non-amblyopic eyes (Table 5). Interestingly, figure 7 shows that there were 13 participants (approximately 1/3rd of the participants) who had slightly better RDA in their amblyopic eye while a small amblyopic deficit was still present in VA. This may have occurred because for all tests, the amblyopic eye was tested first. This combined with the length of time it took for the participants to complete the RDA charts may have resulted in some participants losing interest and not trying as hard for the non-amblyopic eye. This is a problem that was identified by Kaiser (2009) in their study regarding VA assessment. These authors suggested that accurately ascertaining vision is influenced by several factors, including developmental and cognitive factors, as well as the design of the test chart. It is also possible that using three RDA charts per eye was too time consuming for this age group and consequently, reduced the reliability of the results for the second (or in our case, non-amblyopic eye) eye. It is also plausible that the amblyopic eye RDA improved faster and beyond the non-amblyopic eye even though a deficit was still present in VA. This was also suggested in a previous study by Simmers et al. (1999) in a group of functional amblyopes tested on VA, CS, and vernier acuity.

5.1.2 Relationship Between Amblyopic Deficit With RDA And VA

This is the first study to examine the relationship between magnitude of the depth of amblyopia with the Manchester RDA charts and ETDRS VA chart. In this sample of children

with amblyopia there was a moderate relationship between the magnitude of the amblyopic deficit in RDA and VA, $r(35) = -0.42$, p (2-tailed) < 0.05. The negative correlation was expected because logMAR VA and log RDA are scored inversely. Furthermore, 17.4% of the total variation in RDA can be explained by the linear relationship between RDA and VA (as described by the regression equation). Similarly, Subramanian et al. (2012) found significant correlations between two crowded hyperacuity stimuli and optotype acuity among amblyopic subjects (1 deg radius 16 RF stimuli: Spearman r = 0.59, p = 0.013; 0.5 deg radius 8 RF stimuli: Spearman r = 0.83, p = 0.001) and among all participants (1 deg radius 16 RF stimuli: Spearman r = 0.53, p < 0.001; 0.5 deg radius 8 RF stimuli: Spearman r = 0.72, p < 0.001). The aforementioned authors converted their radial deformation values into logMAR to aid in their comparison to VA, thus resulting in a positive correlation. In comparison, Wang (2001) found no significant correlation between VA and the radial deformation acuity for normal adult subjects. This author suggested that this was not surprising because the spatial frequency content of the stimulus used in their study was centered around 5 cpd, well below the resolution limit of all subjects.

Figure 7 demonstrates that the RDA deficit was roughly proportional to the deficit in VA. A similar finding was reported by Subramanian et al. (2012) who found that the loss of hyperacuity for 0.5 deg 8RF patterns was proportional to or greater than loss of optotype acuity in a group of strabismic amblyopes. In the present study, what can be inferred from the proportionality of the deficits is that when amblyopia is treated, the RDA deficit disappears in line with VA deficit. This result should be unsurprising as there have been a number of studies that have reported that other visual functions including CS and vernier acuity, improve with the treatment of amblyopia (Koskella & Hyvarinen, 1986; Levi et al., 1997; Moseley et al., 2006; Simmers & Gray, 1999; Simmers et al., 1999; Sjostrand, 1981). With

this said, the deficits in RDA and VA were not directly proportional. This result could be expected because as was noted by Simmers et al. (1999), not all visual functions are affected equally in amblyopia, nor do they improve with treatment at the same rate.

5.1.3 Relationship Between Amblyopic Deficit With RDA And CS

This was also the first study to evaluate the relationship between the magnitude of the depth of amblyopia with the Manchester RDA charts and Pelli-Robson CS chart. In this sample of children with amblyopia, there was a small relationship between the amblyopic deficit with RDA and CS ($r(35) = 0.27$, p (2-tailed) = 0.117) (Figure 8). The coefficient of determination was $r^2 = 0.07$ (Figure 8). This means that only 7% of the total variation in RDA can be explained by the linear relationship between RDA and CS (as described by the regression equation). The other 93% of the total variation in RDA remains unexplained. This figure demonstrates that in general, even if a participant demonstrated good Pelli-Robson CS in the amblyopic eye, they could still have a large amblyopic deficit in RDA. Unfortunately, no other study has examined the relationship between RDA and CS in amblyopic subjects. With this said, one study by Wang (2001) reported no significant correlation between letter contrast threshold and the detection threshold for RDA at a modulation frequency of 8 cycles/2π in a group of normal adults. The lack of a relationship between RDA and CS should not be surprising as the Pelli Robson chart was not able to detect amblyopia in most of the sample even though a deficit was present in VA and/or RDA. Additionally, both Wang (2001) and Wilkinson et al. (1998) have suggested that RDA is unaffected by contrast reduction. Thus, one would expect to find little relationship between the results of these two visual functions.

5.1.4 Relationship Between Amblyopic Deficit With VA And CS

The relationship between the magnitude of the depth of amblyopia with the ETDRS chart and Pelli-Robson CS chart was examined. In this sample of children with amblyopia, there was a moderate relationship between the deficits in VA and CS ($r(34) = -0.53$, p (2-tailed) < 0.01) (Figure 9). The coefficient of determination was $r^2 = 0.28$. This means that 28% of the total variation in VA can be explained by the linear relationship between VA and CS (as described by the regression equation). The other 72% of the total variation in VA remains unexplained. A number of other authors have reported similar findings. McKee et al. (2003) found a moderate increase in contrast threshold (exponent =0.30) with increasing amblyopia in a large group of functional and deprivation amblyopes. These authors suggested that the correlation between CS measured with Pelli-Robson and optotype acuity measured with ETDRS VA chart was moderately strong but accounted for 34% of the variance in the two measures (r=0.61). Rydberg et al. (1997) also reported a significant correlation between Snellen VA and CS tested with the Pelli-Robson chart in a group of adult strabismic and mixed amblyopes (r=0.587, p<0.01). In comparison, Moseley et al. (2006) in a group of 3 to 8 year old functional amblyopes found that for those subjects with relatively poor amblyopic eye logMAR acuities (approx. >0.9), there was evidence of a related loss of CS tested with the Pelli-Robson charts. When the VA deficit was less severe (approx. <0.9 logMAR) there was little evidence of any relation to log CS. These authors also reported that log CS was weakly though significantly correlated with logMAR acuity for all VA's better than 0.9 (r= -0.19, 95% CI: -0.28 to -0.10) whereas for all VA's of 0.9 or poorer, log CS was markedly and significantly correlated with VA (r=-0.72, 95% CI: -0.83 to -0.53). This result was interesting when compared to the present study. The present study had a stronger correlation between VA and CS in a sample comprised of older, treated amblyopes (median amblyopic eye VA +

0.24 logMAR). There are a number of reasons why there was a difference in results between this study and the aforementioned one. First, the study by Moseley et al. (2006) used a younger age group. Consequently, it is possible that their results were less reliable. Secondly, Moseley et al. (2006) used the Bailey-Lovie VA chart whereas the present study used the ETDRS VA chart. Although these charts are similar, they are not identical. Thirdly, Moseley et al. (2006) considered a response as correct if a child gave an answer that was similar to the correct answer during CS testing. For example, if a child thought a C was an O, they scored that response as correct. This may have also made their scores less accurate. All of the above could have affected their VA and CS results thus changing the strength of their correlation.

It bears noting again that most of the sample used in the present study were either undergoing treatment at the time of testing or had been previously treated for their amblyopia. Consequently, it is unknown what the relationship between these two visual functions would have been if the sample had been comprised of untreated amblyopes. A number of authors have examined the recovery of CS and VA during amblyopia treatment (Abrahamsson & Sjöstrand, 1988; Moseley et al., 2006; Sjostrand, 1981). These authors have noted that although both CS and VA improve with treatment, improvement in one function is not highly predictive of the other.

5.1.5 Relationship Between Gender And RDA

The relationship between gender and amblyopic deficit measured on the VA, RDA, and CS tests was examined. According to our review of the literature, our study was the first to examine the relationship between gender and RDA deficit. The present study found no significant difference between the median amblyopic deficit of boys and girls (VA: $U(35) = 138.5$, $z = -0.479$, $p = .63$ / RDA: $U(35) = 117.5$, $z = -1.172$, $p = .24$ / CS: $U(35) = 137$, $z = -0.719$, $p = .47$).

Unlike the present study, Robaei, Rose, Ojaimi, Kifley, Huynh, & Mitchell (2005) reported a statistically significant difference in VA between 6 to 12 year old Australian bys and girls. These authors noted that although this difference reached statistical significance, the actual difference was less than one logMAR letter and in the right eye only. Consequently, this difference was deemed not clinically important. Pan et al. (2009), in a study that attempted to determine normative data for monocular VA, reported that boys performed significantly better than girls in the 5 to 6 year age group on the HOTV VA chart. Finally, Brown & Yap (1995) in a sample of 16 to 64 year old participants reported better VA for males than females, although the difference only reached significance for the right eye.

Others have looked at gender differences and CS. Gwaizda et al. (1997) in their study examining changes in CS from infancy to adulthood reported that there were no gender differences for peak spatial frequency, sensitivity at the peak of the CSF or in spatial frequencies below the peak frequency.

5.1.6 Relationship Between Age And RDA

The present study sought to examine the relationship between age and the results of the VA, RDA and CS tests. The results suggest that there was no relationship was between age and performance for any of the three tests used in this study (Table 7). Older children did not score significantly better on any of the three tests than did younger children. Furthermore, there was no relationship between age and size of amblyopic deficit for any of the three tests (Table 8). This finding was not surprising as most of the children in the age group sampled would have been treated previously or were being treated for amblyopia at the time of the examination.

Unlike the present study, Subramanian et al. (2012) reported a significant change in mean radial deformation hyperacuity from 3 to 17 years of age in their control group. This

may have occurred because these authors used younger children in their sample. Previous research has shown rapid improvement in global hyperacuity during the first 5 years of life, reaching the adult range at 7.5 years (Wang et al., 2009). The present study used participants who were either close to or at adult range, perhaps explaining why the present study did not identify an age effect. It is also possible that the change in radial deformation hyperacuity by Subramanian et al. (2012) may have been due to the difference in stimulus used between the two studies.

With respect to VA, Dobson et al. (2009) reported a significant effect of age on mean VA ($p < 0.001$) tested on the ETDRS VA chart in a large group of emmetropic 5 to 12 year old children. Post hoc analysis (with Bonferroni correction) indicated a significant difference between the 5-year age group and all other age groups. This result may have differed from the present study because they had 5 year olds in their sample and this group's VA was significantly different than the other age groups. Finally, Elliott & Whitaker (1991) reported a significant age effect in their sample of participant's age 10 to 80 years of age. These authors also found a significant age effect for logMAR VA with the oldest group having a lower level of acuity. This study used a much larger age range therefore contributing to the age effect.

In comparison to the present study, Leat & Wegmann (2004) reported a significant difference between the CS of 6 to 8 year olds and adults age 23 to 27 years of age when tested with the Pelli-Robson chart. The mean log CS for these groups was 1.68 log and 1.79, respectively. These are well below the median (1.95 log) found in the present study.

5.1.7 The Manchester RDA Charts And Children

The accuracy of vision assessment is influenced by several factors, including developmental and cognitive factors, light intensity; number, size, contrast, and shape of the optotypes; and the design of the test chart (Kaiser, 2009). The choice of chart ideally should

not influence the outcome of the measurement. The results of the present study suggest that the Manchester RDA charts can be used in most but not all children of this age group (Table 9). With this said, the average testing duration for the Manchester RDA charts was 10 minutes, 8 seconds (range of 5:34 to 16:03). The present study did not assess the cooperation or testing duration for either the ETDRS or Pelli-Robson charts. Two papers have reported the testing duration for the ETDRS VA chart using amblyopes. Only one paper was found that reported testing duration for Pelli-Robson CS chart. Laidlaw, Tailor, Shah, Atamian, & Harcourt (2008) reported that in their large sample of 5 to 10 year old functional amblyopes, the median testing duration for the ETDRS chart was 85 seconds. In comparison, Laidlaw, Abbott, & Rosser (2003) had previously reported a median of 60 seconds for testing duration of the ETDRS using a similar sample of functional amblyopes age 5 to 9 years. Owsley (2003) reported the test duration of the Pelli-Robson CS chart. They reported that testing duration ranged from three to five minutes in normal control subjects. Given the limited time a clinician has to examine a patient, along with the limited attention span children have, the Manchester RDA charts may be too time consuming to use in this age group. Future research could determine if it would be more efficient to use only one or two charts per eye rather than the prescribed six or the modified method of three per eye, as was done in the present study.

5.1.8 Test-Retest Variability Of The Manchester RDA Charts

Prior to this study, the Manchester RDA charts had not been used in amblyopic subjects. Furthermore, these charts had yet to be evaluated for TRV. Consequently, the authors of the present study decided to evaluate the TRV for each of the charts (RDA, VA, CS) used in this study.

The TRV for the Manchester RDA charts, based on 80% limits of agreement, was 0.43 log for the amblyopic eyes and 0.34 log for the non-amblyopic eyes. This means that the

criterion for a clinically meaningful change in RDA for children 6-12 years of age using the Manchester RDA charts is +/-3 to 4 lines. This represents a fairly large amount of variability between testing sessions. This may have occurred because the test was time-consuming, requiring approximately 10 minutes to complete. Another possibility is that as each eye was tested three times, the children may have lost the interest and subsequently, attended less over the course of testing resulting in more variation in scores. As was stated previously, accurately determining vision can be influenced by developmental and cognitive factors, as well as the design of the test chart. To ensure good focus during testing future research should consider employing only one or two charts per eye when testing children rather than the three used in this study. Finally, there was a large time period between testing sessions (7 to 14 months). Although this length of time may assist in avoiding changes in TRV from familiarity with the test, it can also allow time for amblyopic eye regression, improvement in RDA secondary to treatment, or changes due to maturation (better cooperation with aging). These factors combined with the small sample size (n=10) made the TRV more prone to variability.

In comparison to RDA, the TRV for the ETDRS chart agreed fairly well with previous research whereas the Pelli-Robson charts agreed very well with established norms. The TRV for the ETDRS chart in the present study was +/- 0.36 for the amblyopic eyes and +/- 0.06 for the non-amblyopic eyes. This means that the criterion for a clinically meaningful change in VA for children 6-12 years of age using the ETDRS chart was 3 letters for the non-amblyopic eye and 18 letters for the amblyopic eye. Previous literature has suggested a range from +/-0.10 to +/-0.14 logMAR in amblyopic children age 5 to 12 years and +/-0.07 to +/-0.20 logMAR in normal children and adults (Arditi & Cagenello, 1993; Laidlaw et al., 2003; Laidlaw et al., 2008; Manny et al., 2003; Rosser et al., 2001; Rosser et al., 2003; Rosser et

al., 2003; Stewart et al., 2006). The larger amblyopic eye TRV in the present study may have been due to variability induced by the extended period between testing sessions along with the small number of participants retested. This extended period between sessions allowed sufficient time for clinically significant changes in VA to occur either from regression or treatment. It should be noted that in our sample of retested participants, one subject suffered a large, clinically significant regression in amblyopic VA after poor compliance with treatment while another had a clinically significant improvement in VA in either eye with more consistent wear of their refractive correction. Another participant improved nine optotypes in their amblyopic eye with occlusion treatment. These factors may have affected the TRV of the amblyopic eye resulting in a larger value. It is possible that if the time between testing sessions was reduced, the TRV may have been smaller. With this said, any treatment during this period may result in a change in VA thus causing variability in results from one session to another. Further researchers may wish to consider using amblyopes who are not undergoing treatment at the time of testing. Further, a larger sample size may make the TRV less susceptible to those few patients who suffer a large regression, as these subjects tend to be in the minority.

The TRV for the Pelli-Robson chart in the present study was +/- 0.15 log for both the amblyopic and non-amblyopic eyes. This means that the criterion for a clinically meaningful change in CS for children 6-12 years of age using the Pelli-Robson charts was one letter triplet for either eye. These results agree well with previous literature using the Pelli-Robson chart. Previous research has suggested a range from +/-0.15 to +/-0.20 log (Elliott et al., 1990; Haymes et al., 2006; Lovie-Kitchin, 2000; Simpson & Regan, 1995). It should be noted that all of the aforementioned CS studies used normal adults. Only one study was found that tested TRV in amblyopes using the Pelli-Robson chart (McKee et al., 2003). Unfortunately,

these authors did not use the Bland Altman method. These authors used correlations for their comparison and found the Pelli-Robson had a Pearson correlation of 0.45 and a Spearman correlation of 0.67.

In summary, the TRV of the ETDRS chart and Pelli-Robson charts agree fairly well with previous research. The TRV of the Manchester RDA charts for amblyopic children 6-12 years of age was +/-3 to 4 lines. Although it is not possible to directly compare the TRV's of the aforementioned charts directly, it is obvious that the RDA charts appear to have more inter-session variability for both the amblyopic and non-amblyopic eyes. With this said, the ETDRS charts have the advantage of being familiar to the participants as they use it at every eye clinic appointment and it uses stimuli with which they are very familiar (optotypes). These factors may have resulted in better TRV for this chart. The Pelli-Robson charts also use letters and are very quick to use. This may have also resulted in better TRV. In comparison, the Manchester RDA charts use an unfamiliar stimulus presented in a fashion they have never seen prior to their testing session. Furthermore, these charts take a longer time to complete and require good focus and attention. These factors result in a greater chance of losing the child's attention and thus may have led to greater variability in the Manchester RDA charts TRV.

5.1.9 Conclusion

The measurement of VA plays a primary role in clinical assessment of ophthalmic disease, response to treatment, and is the primary outcome of most clinical trials. VA is a quantitative measure of vision that is tested under highly ideal conditions that do not reflect real world conditions. Even more importantly, VA is only one facet of vision. This is of primary concern in orthoptics because amblyopia affects visual functions other than VA. Unfortunately, the diagnosis and monitoring of amblyopia treatment are based on

improvement in high contrast VA alone. It is not uncommon for clinicians to tell a family that their child's amblyopic eye VA has become equal with the non-amblyopic eye and thus treatment can be concluded, suggesting that their amblyopia has been successfully treated. What the results of the present study and others have found is that amblyopia is a multifaceted problem that VA alone cannot fully describe (McKee et al., 2003). Even when amblyopia appears to be treated, there may still be deficits in other visual functions (Simmers et al., 1999). Furthermore, Hess et al. (1999) and Hess (2001) have suggested that the fundamental deficit in amblyopia is positional uncertainty, a term encompassing hyperacuity. Other authors have suggested that there are distinct problems in each type of amblyopia and treatment should be directed at these problems (McKee et al., 2003; Simmers et al., 1999). Simmers et al. (1999) also suggested that it is imperative that clinicians understand the diverse reduction in visual performance that occurs in amblyopic eyes and the need to monitor other aspects of visual function during treatment of amblyopia. The results of the aforementioned studies support the need for other tests in the treatment of amblyopia; in particular, a hyperacuity test appears to be indicated. Previous research has suggested that Vernier acuity is highly correlated with VA and thus the results of one can be predicted from the other (McKee et al., 2003). Furthermore, these authors reported that the loss of vernier was directly proportional to the loss of VA. Both the present study and a study by Subramanian et al. (2012) show that RDA has a moderate relationship with VA. This may make this form of hyperacuity of potential use in the diagnosis and treatment of amblyopia. The results of this study demonstrated that the Manchester RDA charts could detect most cases of amblyopia. However, the Manchester RDA charts were time consuming and the TRV may be too large for this test to be considered reliable in this age group. It may be that a

reduction of charts tested per eye may make the test more reliable and thus useful in the detection of amblyopia and the monitoring of its treatment.

5.1.10 Limitations

There are a number of limitations associated with the present study. First, this study did not use an age matched control group. This reason for this choice was two fold. First, the sample we recruited was from the IWK Health Centre. Consequently, we did not have direct access to children with normal vision. Second, amblyopia is defined based on asymmetry of VA and not VA compared to normative data. The benefit of a control group would have been the ability to compare both the amblyopic and non-amblyopic eye results against normative values. In particular, this would have been useful information as some authors have reported subtle deficits in the non-amblyopic eye.

The duration of RDA testing was not measured in the first ten participants because it was not originally part of the research protocol. As testing proceeded, it seemed as though the test was time consuming. The length of time to complete the testing was therefore measured from the eleventh participant onward. The duration of testing for VA and CS were also not recorded in any participants.

The participant cooperation was recorded only during RDA testing and not during VA and CS testing.

Neither the room lighting nor the illumination of the ETDRS chart was measured using a light meter prior to the start of recruitment or at each testing session. This also was not part of the original research protocol and thus was not done. This is an important limitation because it is possible that the room lighting was not consistent. Additionally, two of the participants in the present study had their CS tested in a different area than the others. This may have affected their CS results, as the lighting may not have been consistent in each

area. It is uncertain whether the ETDRS chart used in the study was properly calibrated because this was not confirmed with a light meter.

The length of time between testing sessions was large ranging from 9 to 14 months. This occurred because a second testing session was not initially part of the research proposal. After reevaluating the study purpose, the author instituted a second testing session to determine the TRV of the Manchester RDA charts. This required the author to await new ethical approval and then re-contact the study participants. Unfortunately, this process resulted in both an inconsistent and large interval between testing sessions. These limitations make it difficult to determine if the changes were due to maturity of the visual system, maturation resulting in better cooperation, or practice. It should also be noted that only a small sample of participants were retested (n = 10). This makes it difficult to generalize the results of the study to a larger population of amblyopes.

The present study also has a number of other limitations that should to be taken into account. The small sample size (n=35) recruited for the present research makes it difficult to generalize the results to a larger population. One clinician examined all participants. Due to this, it was not possible to evaluate inter-observer variation. Alternatively, this could be seen as a strength of the study because only one examiner did all testing under mostly identical conditions using the interpolated scoring method, thus avoiding inter-tester variability. Another possible limitation is that the examiner was not blinded to the participant's VA, type of amblyopia, or current and previous treatments. This is because prior to recruitment, all of the participants were patients of the primary investigator at the IWK Health Centre Eye Clinic. This may have introduced bias.

The testing of VA, RDA and CS can be challenging in a pediatric population because children are prone to greater variability in their scores due to level of attention, fatigue, and

determination. To counter this potential limitation and to avoid bias from these factors, all participants were given encouragement during VA, RDA, and CS testing. Unfortunately, it is not possible to ensure that participants maintained the exact suggested distance from each chart because the children are prone to move around. This may make the results less reliable than if adults were used. The age group in the present study was 6-12 years. Due to this, we cannot generalize these results to older patients with amblyopia.

Another possible limitation was that the diagnostic criteria for anisometropia might not have allowed for a large enough anisometropic difference between the eyes. Consequently, some of the participants may have been classified as "anisometropic amblyopes" when in actuality they were strabismic amblyopes. Finally, this study used treated amblyopes in its sample. Consequently, the results of this study cannot be generalized to deeply amblyopic participants.

5.1.11 Future Research

The results of the present study indicate that more research is warranted regarding RDA and amblyopia. Future research should consider using one or two RDA charts per eye when testing children, rather that the standard six or the modified three per eye. This may allow for better reliability of scores, as the test duration will be shorter. Future research should also consider randomizing which eye is tested first. This may help alleviate the effect of fatigue on the results during testing of the second eye. Future research may also consider gathering RDA scores in normal, healthy children to allow comparisons between children with ocular pathology against normal controls of the same age group. It would also be interesting to determine the TRV for the Manchester RDA charts in a group of healthy children. This would also allow comparisons between those with amblyopia and those without. A shorter time frame between test sessions (1 month) when assessing TRV would

reduce the risk of confounding results secondary to maturation.

Future studies should also assess RDA in a sample of untreated amblyopes from the beginning to the end of amblyopia treatment. This would allow researchers to observe the changes in RDA with treatment and generalize the results to a larger population of amblyopes.

It would be interesting to determine if there is a crowding effect for the stimulus used in the Manchester RDA charts. One previous author suggested that the crowding effect did not occur in RDA. It would be useful to determine if this was accurate and whether this result is unchanged using the Manchester RDA charts.

Future research may wish to consider novel ways of presenting the RDA stimulus to improve its viability in children. One option would be to create an app on the Apple iPad. The app could be touch-sensitive and could give positive reinforcement when the child correctly identifies the deformed stimulus and encouragement when they do not. Another way to improve the child's compliance with the test would be to include practice sessions using the Manchester RDA charts prior to the start of a study so that the children enrolled are familiar with the test and its stimulus.

Appendix A. Sample Assent Form

INFORMATION AND ASSENT FORM

Title of Study: The Manchester Radial Deformation Acuity Chart: A New Clinical Test for Amblyopia? (In other words: Can this new test tell us if someone has a "lazy eye"?)

Principal Investigator (Graduate Student):
Michael Betts, BSc, OC(C), COMT
Dalhousie University, Masters of Clinical Vision Science Student
IWK Health Centre, Certified Orthoptist, Certified Ophthalmic Medical Technologist

Co-Principal Investigator (Co-Supervisor):
Karen McMain, BA, OC(C), COMT
Program Director
Clinical Vision Science Program
Dalhousie University
Chief of Orthoptics
IWK Health Centre

Co-Principal Investigator (Co-Supervisor):
Dr. Paul Artes
Associate Professor & Foundation Scholar in Glaucoma Research
Ophthalmology and Visual Sciences
Dalhousie University

Why are we doing this study?
Research has shown that people with a "lazy eye" have difficulty seeing well. How well a person sees is usually tested by having a person read letters on a chart from different distances. But vision is more than just seeing letters. We want to find out if a new kind of chart can help us measure how well people with a "lazy eye" see.

The new chart uses groups of circles instead of letters. One of the circles in the group will be bumpy. People are very good at judging the shape of curved objects like a face or a ball. Researchers think that having a "lazy eye" makes it more difficult to tell if a circle has a bumpy edge or if it is smooth. We want to know if having a "lazy eye" makes it difficult to pick a bumpy circle out of a group of smooth circles.

What will happen during this study?
You will come to the IWK and spend one hour with the researchers. The researcher will test your eyes by asking you to look at different shapes and pictures and tell us what you see. Some of these tests will be almost the same as the ones you have probably had at the Eye Clinic, and a few will be new. **NO** eye drops will be used for the research and we don't need to touch your eye for any tests, but we will need to cover one eye at a time for some tests.

Are there any good or bad things about this study?
There should be nothing bad about being in this study. There will be no eye drops used in the exam. This study may not help you, but it may give the researchers some information that may help people with amblyopia ("lazy eye") in the future.

Who will know about what I did in this study?
No one except the researchers will know you are in this study unless you want to tell them. Your name, your study forms, and your chart will only be seen by people involved in the study.

Do I have to be in this study?
You do not have to be in this study. No one will be mad at you and it will not affect how anyone in the Eye Clinic will look after you. If you don't want to be in this study, tell us. Even if you say yes now, you can change your mind later. Being in this study is totally up to you.

What if I have questions?
You can ask questions about the study at any time, now or later. You can talk to your parents about things you don't understand. You can also ask Michael or Steve. You can call Steve at 470-2741 or email him at steve.van-iderstine@iwk.nshealth.ca.

Appendix B. Sample Authorization Form

INFORMATION AND AUTHORIZATION FORM

Research Title: The Manchester Radial Deformation Acuity Chart: A New Clinical Test for Amblyopia?

Principal Investigator (Graduate Student):
Michael Betts, BSc, OC(C), COMT
Dalhousie University, Masters of Clinical Vision Science Student
IWK Health Centre, Certified Orthoptist, Certified Ophthalmic Medical Technologist

Co-Principal Investigator (Co-Supervisor):
Karen McMain, BA, OC(C), COMT
Program Director
Clinical Vision Science Program
Dalhousie University
Chief of Orthoptics
IWK Health Centre

Co-Principal Investigator (Co-Supervisor):
Dr. Paul Artes
Associate Professor & Foundation Scholar in Glaucoma Research
Ophthalmology and Visual Sciences
Dalhousie University

Introduction
Your child is being invited to take part in the research study named above. This form provides information about the study. Before you decide if you want your child to take part, it is important that you understand the purpose of the study, the risks and benefits and what your child will be asked to do. Your child does not have to take part in this study. Taking part is entirely voluntary (your choice). Informed consent starts with the initial contact about the study and continues until the end of the study. A staff member of the research team will be available to answer any questions you have. You may decide not to enrol your child or you may withdraw your child from the study at any time. This will not affect the care you or your family members will receive from the IWK Health Centre in any way.

Why are the researchers doing the study?
Research has shown that people with amblyopia ("lazy eye") have difficulty seeing well in one eye. How well a person can see is evaluated by having them read a letter chart from a certain distance. Vision charts are designed with black letters on a white background and testing is done under controlled conditions. Although this is the accepted method for testing visual acuity, there is more to vision than identifying letters. Amblyopia affects vision in a number of ways other than reduction of visual acuity alone.

One of the most striking properties of most natural objects in our environment, for example faces, is curvature. The Manchester Radial Deformation Acuity Chart uses groups of circles instead of letters. One of the circles in the group will be bumpy (distorted). People with normal vision are very good at judging the shape of an object, as well as identifying distortions in shapes of smooth objects. People with amblyopia have poor vision in one eye. Research has shown that people with amblyopia may have difficulty in determining if a circular shape is distorted with their amblyopic eye.

The purpose of the study is to determine how amblyopia affects the ability of a person to make out if a circle is deformed. We want to find out if the Manchester Radial Deformation Acuity Chart can help us assess how well people with an amblyopia can see. If so, this may help us better identify and treat amblyopia.

How will the researchers do the study?
This will be a prospective cross-sectional study. What this means is that this study aims to describe the relationship between a disease (amblyopia) and other factors of interest (visual acuity, radial deformation acuity, and contrast sensitivity) as they exist in children with amblyopia at the IWK Health Centre.

In this study, we are looking for people with amblyopia due to three causes: strabismus (turned eye), anisometropia (different prescriptions in each eye), and mixed. We are looking for a total of 50 participants. All of the research will be conducted at the IWK Health Centre.

What will my child and I be asked to do?

If you are interested in enrolling your child in the study, we will first go over the information and authorization form. You will also be given a copy of this form to keep. If you decide to allow your child to participate and they are considered eligible, you can either perform the testing at the end of his/her current eye exam or another appointment time can be scheduled to perform the testing. When your child arrives for testing, one of the researchers will review this information and authorization form with you again and answer any questions you or your child may have. You will then be asked to sign the authorization form. All testing will be for research purposes only. Testing will take place at the IWK Health Centre Eye Clinic and is expected to take less than one hour.

The testing procedure will include a short eye exam along with contrast sensitivity and radial deformation acuity testing. The eye exam will consist of measuring your child's visual acuity, binocular status (i.e., ability to use your eyes together), ocular alignment (i.e. check if your eyes are straight), fixation, and pupil function. The testing procedures used for this part of the assessment will be the same as those during a regular eye clinic appointment. None of the testing will require touching the eye or the use of eye drops.

Following the eye examination, your child will have their contrast sensitivity and radial deformation acuity assessed. Contrast sensitivity testing will require your child to read letters on a chart until it is too difficult for them to identify the letters correctly. Radial deformation acuity testing will require your child to determine which circle in a group of 5 circles is bumpy. As they move down the chart the task will become more difficult. They will continue

to move down the chart until they can no longer identify which circle is bumpy. Testing of your child's visual acuity, contrast sensitivity, and radial deformation acuity will be done one eye at a time. None of the equipment used or procedures followed pose any risk to your child's well being.

For those who are willing, a second testing session will take place at a later date to allow the assessment of the reliability of the RDA test. At this visit, only visual acuity, contrast sensitivity, and RDA will be assessed. The investigator will call the participant's parent to enquire about interest in participation in a second session.

What are the burdens, harms, and potential harms?
There are few anticipated risks to your child. None of the eye testing requires touching the eye or the use of medications. We may discover that your child has reduced visual acuity that you were not aware of. If this occurs, you will be advised to visit your eye care provider for a thorough examination. Your child's personal information will be kept confidential**.**

What are the possible benefits?
Taking part in this study may be of no help to you or your child personally. What we learn in this study may improve our understanding of how amblyopia affects radial deformation acuity. Also, we may determine that the Manchester Radial Deformation Acuity test may help clinicians in the detection and treatment of future patients with amblyopia.

What alternatives to participation does my child have?
Your child does not have to participate in the study. This is completely optional. If you decide not to enroll your child, your decision will not affect the care that you, your child, or your other family members receive at the IWK Health Centre.

Can I withdraw my child from the study?
If you decide you no longer want your child to participate in the study, you may withdraw your child from the study at any time. This will not affect the care you, your child, or your other family members receive at the IWK Health Centre.

Will the study cost me anything and, if so, how will I be reimbursed?
The study will not cost you anything to participate and you will not be paid for joining the study. With this said, the cost of parking at the IWK Health Centre will be paid for by the researcher. The PI will also pay for fuel mileage for those patients who live outside the Halifax Regional Municipality and are not attending a regularly scheduled eye appointment the same day as participation in the current research.

Are there any conflicts of interest?
There are no conflicts of interest on the part of the researchers or the IWK Health Centre.

What about possible profit from commercialization of the study results?
The researchers will not receive any profit from commercialization of the study results.

How will my privacy be protected?

All personal information collected from your child will be kept private. The only people who will have access to your child's personal information will be those who are involved in conducting the research and the IWK Health Centre research office. Paper records will be kept in a locked area and electronic data will be password-protected. These records will be kept for five years after publication of the results, as required by the IWK Research Ethics Board. If the results of the study are published in the medical literature, no information that could identify your child will be included.

What if I have study questions or problems?
If you have any additional questions about the study, you may contact the principal investigator (Michael Betts) by e-mail at mjbetts@dal.ca or the Eye Care Team Research Associate (Steve Van Iderstine) at (902) 470-2741 or by email at steve.van-iderstine@iwk.nshealth.ca, Monday to Friday between 8:30 a.m. and 4:30 p.m.

What are my Research Rights?

Your signature on the form indicates that you have understood to your satisfaction the information regarding participation in the research project and agree to enroll your child as a subject. In no way does this waive your legal rights nor release the investigator(s), sponsors, or involved institution(s) from their legal and professional responsibilities. If your child becomes ill or injured as a direct result of participating in this study, necessary medical treatment will be available at no additional cost to you. You are free to withdraw your child from the study at any time without jeopardizing the health care your child is entitled to receive.

If you have any questions at any time during or after the study about research in general you may contact the Research Office of the IWK Health Centre at (902) 470-8765, Monday to Friday between 9a.m. and 5p.m.

How will I be informed of study results?
The study results will be available to you once the research is complete. Please indicate below whether you would like to receive a summary of the study results.

Would you like to receive a summary of the study results? Yes _____ No_____

If you checked "yes", please provide your mailing or email address:

_____

_____

_____

Future contact
May we contact you about participating in future studies similar to this one?

Yes _____ No_____

AUTHORIZATION FORM

Study title: The Manchester Radial Deformation Acuity Chart: A New Clinical Test for Amblyopia?

Participant ID: _____
Participant INITIALS: _____

Parental or Guardian Authorization

I have read or had read to me this information and authorization form and have had the chance to ask questions which have been answered to my satisfaction before signing my name. I understand the nature of the study and I understand the potential risks. I understand that I have the right to withdraw my child from the study at any time without affecting my child's care in any way. I have received a copy of the Information and Authorization Form for future reference. I freely agree to have my child participate in this research study.

_____
Name of Participant (Print)

_____ _____
Name of Parent/Guardian (Print) **Signature of Parent/Guardian**

Date: _____ **Time: _____**

STATEMENT BY PERSON PROVIDING INFORMATION ON STUDY
I have explained the nature and demands of the research study and judge that the Parent/Guardian/Participant named above understands the nature and demands of the study.

Name (Print): _____

Signature: _____ Position: _____

Date: _____ Time: _____

STATEMENT BY PERSON OBTAINING CONSENT

I have explained the nature of the consent process and judge that the Parent/Guardian/Participant named above understands that participation is voluntary and that they/their child may withdraw at any time from participating

Name (Print): _____

Signature: _____ Position: _____

Date: _____ Time: _____

Appendix C. Clinical Characteristics Of Participants

ID #	Rx RE	Rx LE	APCT 0.33cm (Diopters)	APCT 6m (Diopters)	Worth-4-dot (0.33cm/6m/ flashlight)	Stereopsis (sec. of arc)
1	+4.00+2.00X080	+4.00+1.25X080	E8	E4	BSV/ RE supp.	75
2	+0.25	+3.50	0	0	BSV/LE supp.	60
3	+3.50+1.25X075	+3.50+2.50X105	LET+E8 (APCT) LET3 (SPCT)	LET4	BSV/BSV/BSV	3000
4	+3.25+0.25X012	+1.25+1.00X170	X4	E2	BSV/BSV/BSV	40
5	-0.75+0.25X160	-0.25+0.25X160	L/AET25 DVD	L/AET16 DVD	Vertical diplopia L/R	0
6	+4.25+0.75X100	+3.75+1.25X080	RET+E10 (APCT) RET5 (SPCT)	RET6	BSV/RE supp.	3000
7	+2.75+1.75X081	+3.50+3.00X110	LX(T)16 DVD	LX(T)18 DVD	BSV/LE supp.	5000
8	+1.50	+4.25+1.00X160	0	0	BSV/BSV/BSV	55
9	+4.25+2.50X108	+4.25+1.75X075	E6	0	BSV/BSV/ partial RE supp. to 4m	300
10	+2.25+2.25X105	+0.25+1.75X085	RET+E6 (APCT) RET2 (SPCT)	RET8	BSV/RE supp.	300
11	+5.75+2.75X085	+4.75+1.00X090	RET+E16 (APCT) RET 8 (SPCT)	RET8	uncrossed diplopia	3000
12	+1.00+1.00X090	+1.00+3.50X100	LET12	LET10	BSV/LE supp.	3000
13	+4.50	+4.00+1.00X080	LET2	R/AX(T)2	Alt. supp./Alt. supp.	3000
14	+3.00+0.75X089	+3.00+1.00X093	LET18	LET18	BSV /Alt. supp.	0
15	+4.50+0.75X180	+4.00+1.50X175	Upper-	0	bifocal-	5000

	Bif. +1.00	Bif. +1.00	RET20 Bif.- RET+E14 RET6		BSV/BSV	
16	+6.50	+5.75	RET4	RET2	BSV/BSV	3000
17	None	None	R/AXT30	R/AXT30 RhypoT1	Alt. supp/Alt. supp.	0
18	+1.00+3.00X080	+1.50+3.00X095	LET6 DVD	LXT14	LE supp./LE supp.	0
19	+5.00	+5.00	E4	E2	BSV/BSV/RE supp to 3m (.66)	85
20	+5.50+1.50X195	+7.50+0.75X085	LET4	LET4	BSV/BSV/LE supp. to 6m (.33)	150
21	+0.75+0.25X076	+4.25+1.00X105	E1	LX(T)2	BSV/LE supp.	0
22	+3.00+2.50X105	+3.00+3.50X080	LET4	LET2	BSV/Alt. supp.	600
23	+1.00+0.50X085	+4.50+1.50X110	LET8	LET8	LE supp./LE supp.	0
24	+5.00+0.50X085	+7.50+0.75X035	LET10	LET4	BSV/uncrossed diplopia	170
25	+7.25+1.75X090	+8.50+2.50X080	LET4 LhypoT3	LXT2	BSV/LE supp.	600
26	+6.50	+7.00	E8	E2	BSV/LE supp.	3000
27	+4.75+1.25X090	+4.25+1.50X085	LET+E14 (APCT) LET3 (SPCT)	L/AET12	BSV/LE supp.	5000
28	+5.00	plano	RX(T)20	RX(T)16 RH(T)3	BSV/BSV/RE supp. to 5m (0.40)	300
29	+1.25+0.50+090 Bif. +1.50	+1.25+0.25X090 Bif. +1.50	Upper- LET20 Bif- L/AE(T)12	0	BSV/BSV/LE supp.	75
30	+0.50+0.50X105	+0.50+0.50X100	LET+E20 (APCT) LET6	LET+E18 (APCT) LET6	-	600

			(SPCT)	(SPCT)		
31	+3.75+1.00X090	plano	X1	0	BSV/RE supp.	300
32	None	None	E6	0	None	0
33	+5.00+2.00X082	+4.75+1.75X081	RET+E14 (APCT) RET6 (SPCT)	RET4	BSV/BSV	200
34	+4.50	+6.00	LET10	LET6	LE supp./LE supp.	5000
35	+7.25+1.50X096	+6.50+1.25X090	RET8	RET6	RE supp/RE supp.	0

Rx=prescription of glasses, APCT=alternate prism cover test, SPCT=simultaneous prism cover test, BSV=binocular single vision, LE supp.=left eye suppression, RE supp.=right eye suppression, FTO=full time occlusion, X=exophoria, E=esophoria, LET=left esotroptia, LXT=left exotropia, LX(T)=intermittent left exotropia, RET=right esotropia, RXT=right exotropia, RX(T)=intermittent right exotropia, RHT=right hypertropia. LHT=left hypertropia, DVD=dissociated vertical deviation, Upper=upper segment of glasses, bif.=bifocal segment of glasses, Tx= current treatment

Appendix D. Clinical Classification And Participant Results For VA, RDA And CS

Participant age, clinical classification (strabismic - SA, anisometropic – AA, Mixed – MA) and test results for amblyopic (A) and non-amblyopic (Non-A) eyes.

ID #	Age (yrs)	Type of Amblyopia	VA_A (logMAR)	VA_{Non-A} (logMAR)	RDA_A (log)	RDA_{Non-A} (log)	CS_A (log)	CS_{Non-A} (log)
1	7	AA	.34	-.02	2.43	2.97	1.95	1.95
2	8	AA	.20	-.14	2.80	3.13	1.80	1.95
3	9	SA	.44	.12	2.60	2.53	1.95	1.95
4	8	MA	.12	.08	2.63	2.73	1.80	1.80
5	9	SA	.10	.04	2.77	2.87	1.95	1.95
6	8	SA	.44	.12	2.70	2.93	1.95	1.95
7	11	MA	.46	.14	2.30	2.73	1.95	1.95
8	7	AA	.34	-.06	2.80	2.77	1.95	1.95
9	6	AA	.32	.22	2.83	2.70	1.95	1.95
10	6	MA	.18	.00	2.63	2.53	1.95	1.95
11	7	MA	.12	-.06	2.60	2.40	1.95	1.95
12	6	MA	.34	.12	2.33	2.53	1.95	1.95
13	12	SA	.04	-.08	3.00	2.87	1.95	1.95
14	6	SA	.50	.34	2.53	2.50	1.80	1.95
15	10	SA	.18	.02	2.70	2.53	1.95	1.95
16	7	SA	.18	.02	2.87	2.73	1.95	1.95
17	11	SA	.08	.02	2.70	2.63	1.95	1.95
18	8	SA	.24	.12	2.30	2.47	1.95	1.95
19	9	SA	.24	-.02	2.60	2.87	1.95	1.95
20	10	MA	.42	.14	2.77	2.73	1.95	1.95
21	8	MA	.34	.04	2.53	2.670	1.95	1.95

22	9	SA	.22	.04	2.57	2.67	1.80	1.80
23	8	MA	1.04	.04	1.97	2.70	1.50	1.95
24	9	MA	.32	.04	2.53	2.67	1.95	1.95
25	9	MA	.14	-.06	2.63	2.80	1.95	1.95
26	6	AA	.40	.00	2.83	2.80	1.95	1.95
27	7	SA	.08	.10	2.53	2.47	1.95	1.95
28	11	MA	.06	-.06	2.70	2.90	1.95	1.95
29	7	SA	.02	.02	2.53	2.87	1.95	1.65
30	7	SA	.22	.08	2.93	2.73	1.95	1.95
31	8	AA	.44	-.14	2.47	2.47	1.65	1.95
32	7	AA	.34	-.06	2.73	3.00	1.80	1.95
33	6	SA	.26	.06	2.57	2.77	1.65	1.95
34	7	MA	.04	-.06	2.77	2.77	1.95	1.95
35	7	SA	1.04	.18	2.37	2.70	1.65	1.95

AA=anisomtropic amblyopia, SA=strabismic amblyopia, MA=mixed amblyopia, VAA=amblyopic eye visual acuity, VANA=non-amblyopic eye visual acuity, RDAA=amblyopic eye radial deformation acuity, RDANA= non-amblyopic eye radial deformation acuity, CSA= amblyopic eye contrast sensitivity, CSNA=non-amblyopic eye contrast sensitivity.

Appendix E. Sample Consent Form

INFORMATION AND CONSENT FORM

Research Title: The Manchester Radial Deformation Acuity Chart: A New Clinical Test for Amblyopia?

Principal Investigator (Graduate Student):
Michael Betts, BSc, OC(C), COMT
Dalhousie University, Masters of Clinical Vision Science Student
IWK Health Centre, Certified Orthoptist, Certified Ophthalmic Medical Technologist

Co-Principal Investigator (Co-Supervisor):
Karen McMain, BA, OC(C), COMT
Program Director
Clinical Vision Science Program
Dalhousie University
Chief of Orthoptics
IWK Health Centre

Co-Principal Investigator (Co-Supervisor):
Dr. Paul Artes
Associate Professor & Foundation Scholar in Glaucoma Research
Ophthalmology and Visual Sciences
Dalhousie University

Introduction
You are being invited to take part in the research study named above. This form provides information about the study. Before you decide if you want to take part, it is important that you understand the purpose of the study, the risks and benefits and what you will be asked to do. You do not have to take part in this study. Taking part is entirely voluntary (your choice). Informed consent starts with the initial contact about the study and continues until the end of the study. A staff member of the research team will be available to answer any questions you have. You may decide not to take part or you may withdraw from the study at any time. This will not affect the care you or your family members will receive from the IWK Health Centre in any way.

Why are the researchers doing the study?
Research has shown that people with amblyopia ("lazy eye") have difficulty seeing well one eye. How well a person can see is tested by having them read a letter chart from a certain distance. Although this is the usual way of testing vision, we understand that there is more to seeing than recognizing letters. Amblyopia affects vision in a number of different ways.

One of the most common properties of many natural objects in our environment is curvature. The Manchester Radial Deformation Chart uses groups of circles instead of letters. One of

the circles in the group will be distorted (bumpy). People with normal vision are very good at judging the shape of an object, as well as identifying distortions in shapes of smooth objects. People with amblyopia have poor vision in one eye. Research has shown that people with amblyopia in one eye may have difficulty in determining if a circular shape is distorted with that eye.

The purpose of the study is to determine how amblyopia affects the ability of a person to make out if a circle is deformed. We want to find out if the Manchester Radial Deformation Chart can help us assess how well people with a "lazy eye" see. If so, this may help us better identify and treat amblyopia.

How will the researchers do the study?
This will be a prospective cross-sectional study. What this means is that this study aims to describe the relationship between a disease (amblyopia) and other factors of interest (visual acuity, radial deformation acuity, and contrast sensitivity) as they exist in children with amblyopia at the IWK Health Centre.

In this study, we are looking for individuals with amblyopia due to three causes: strabismus (turned eye), anisometropia (different prescriptions in each eye), and mixed. A total of 50 participants will be recruited. All of the research will be conducted at the IWK Health Centre.

What will I be asked to do?
If you are interested in enrolling in the study, we will first go over the information and consent form. If you decide to participate and are considered eligible, you can either perform the testing at the end of your current eye exam or an appointment time to perform the testing can be scheduled. When you arrive for testing, one of the researchers will review this information and consent form with you again and answer any questions you may have. You will then be asked to sign the consent form. All testing will be for research purposes only. Testing will take less than one hour.

The testing will include a short eye exam along with contrast sensitivity and radial deformation acuity testing. The eye exam will consist of the same tests you would have during your regular eye appointment. You will be asked to sit in a chair, read some letters, and look at some pictures and shapes. The researcher will also look at your eyes with a light. None of the testing will require touching your eyes or the use of eye drops.

Following the eye examination, you will have your contrast sensitivity and radial deformation acuity assessed. Testing of your visual acuity, contrast sensitivity, and radial deformation acuity will be done one eye at a time. None of the equipment used or procedures followed pose any risk to your well being.

Some participants will be asked if they are willing to take part in a second testing session. If willing, this can be scheduled at the time of the initial visit. If not, the investigator will call the participant to arrange a convenient time for the participant. The second visit will take less than 30 minutes and will involve a repeat assessment of visual acuity, contrast sensitivity, and RDA only.

What are the burdens, harms, and potential harms?
There are very few anticipated risks. None of the eye testing requires touching the eye or the use of medications. You may discover that you have reduced visual acuity that you were not aware
of. If this occurs, you will be advised to visit their eye care provider for a thorough examination. There is also a risk that someone may learn that you participated in the study without your permission. We will protect your personal information to prevent this from happening. Your name will not be used in any reports about the study.

What are the possible benefits?
Taking part in this study may be of no help to you personally. What we learn in this study may improve our understanding of how amblyopia affects radial deformation acuity. Also, we may determine that the Manchester Radial Deformation Acuity test may help clinicians in the detection and treatment of amblyopia.

What alternatives to participation do I have?
You do not have to participate in the study. This is completely optional. If you decide not to participate, your decision will not affect the care that you or your family receives at the IWK Health Centre.

Can I withdraw from the study?
You may withdraw from the study at any time. This will not affect the care you or your family receives at the IWK Health Centre.

Will the study cost me anything and, if so, how will I be reimbursed?
The study will not cost you anything to participate and you will not be paid for joining the study. With this said, the cost of parking at the IWK Health Centre will be paid for by the researcher. The PI will also pay for fuel mileage for those patients who live outside the Halifax Regional Municipality and are not attending a regularly scheduled eye appointment the same day as participation in the current research.

Are there any conflicts of interest?
There are no conflicts of interest on the part of the researchers or the IWK Health Centre.

What about possible profit from commercialization of the study results?
The researchers will not receive any profit from commercialization of the study results.

How will my privacy be protected?
All personal information collected from you will be kept private. The only people who will have access to your personal information will be those who are involved in conducting the research and the IWK Health Centre research office. Paper records will be kept in a locked area and electronic data will be password-protected. These records will be kept for five years after publication of the results, as required by the IWK Research Ethics Board. If the results of the study are published in the medical literature, no information that could identify you will be included.

What if I have study questions or problems?

If you have any additional questions about the study, you may contact the principal investigator (Michael Betts) by e-mail at mjbetts@dal.ca or the Eye Care Team Research Associate (Steve Van Iderstine) at (902) 470-2741 or by email at steve.van-iderstine@iwk.nshealth.ca, Monday to Friday between 8:30 a.m. and 4:30 p.m.

What are my Research Rights?
Your signature on the form indicates that you have understood to your satisfaction the information regarding participation in the research project and agree to participate as a subject. In no way does this waive your legal rights nor release the investigators, sponsors, or involved institutions from their legal and professional responsibilities. If you become ill or injured as a direct result of participating in this study, necessary medical treatment will be available at no additional cost to you. You are free to withdraw from the study at any time without jeopardizing the health care you are entitled to receive.

If you have any questions at any time during or after the study about research in general you may contact the Research Office of the IWK Health Centre at (902) 470-8765, Monday to Friday between 9a.m. and 5p.m.

How will I be informed of study results?
The study results will be available to you once the research is complete. Please indicate below whether you would like to receive a summary of the study results.

Would you like to receive a summary of the study results? Yes _____ No_____

If you checked "yes", please provide your mailing or email address:

_____

_____

_____

Future contact
May we contact you about participating in future studies similar to this one?

Yes _____ No_____

CONSENT FORM

Study title: The Manchester Radial Deformation Acuity Chart: A New Clinical Test for Amblyopia?

Participant ID: _____

Participant INITIALS: _____

PARTICIPANT CONSENT
I have read or had read to me this information and consent form and have had the chance to ask questions which have been answered to my satisfaction before signing my name. I understand the nature of the study and I understand the potential risks. I understand that I have the right to withdraw from the study at any time without affecting my care in any way. I have received a copy of the Information and Consent Form for future reference. I freely agree to participate in this research study.

Name of participant (Print): _____

Participant Signature: _____

Date: _____ Time: _____

STATEMENT BY PERSON PROVIDING INFORMATION ON STUDY
I have explained the nature and demands of the research study and judge that the participant named above understands the nature and demands of the study.

Name (Print): _____

Signature: _____ Position: _____

Date: _____ Time: _____

STATEMENT BY PERSON OBTAINING CONSENT

I have explained the nature of the consent process to the participant and judge that they understand that participation is voluntary and that they may withdraw at any time from participating

Name (Print): _____

Signature: _____ Position: _____

Date: _____ Time: _____

Appendix F. Sample Inclusion/Exclusion Criteria Poster

The Manchester Radial Deformation Acuity Chart: A New Clinical Test for Amblyopia?

Principal Investigator (Graduate Student): Michael Betts, BSc, OC(C), COMT

Inclusion Criteria- All Groups

- 6 to 12 years of age.
- Diagnosis of anisometropic, strabismic, or mixed forms of amblyopia, who do not have any of the listed exclusion criteria.
- Must have 2 (10 optotypes) or more lines (or had prior to treatment) of intraocular difference of vision between their amblyopic and non-amblyopic eye on the ETDRS logMAR acuity chart.
- Visual acuity can be no worse than 6/60.
- Wearing prescribed refractive correction.
- Cycloplegic refraction in the last 2 years.
- Ability to understand English.

Inclusion Criteria-Anisometropic Amblyopia Group

- Amblyopia in the presence of anisometropia of ≥0.5D of spherical equivalent or ≥1.50D of difference in astigmatism in any meridian, with no measureable heterotropia at distance or near fixation, which persisted after at least 4 weeks of spectacle correction.

Inclusion Criteria-Strabismic Amblyopia Group

- Amblyopia in the presence of either a heterotropia at distance and/or near fixation or a history of strabismus surgery (or botulinum) and in the absence of refractive error meeting the criteria below for mixed amblyopia.

Inclusion Criteria-Mixed Amblyopia Group

- Amblyopia in the presence of either a heterotropia at distance and/or near fixation or a history of strabismus surgery (or botulinum) and anisometropia of ≥1.00D spherical equivalent or ≥1.50D of difference in astigmatism in any meridian, which persisted after 4 weeks of spectacle correction.

Exclusion Criteria-All Groups

- Clinical evidence of ocular, neurological, incapacitating systemic disease.
- Presence of any notes on the clinical chart or verbal history of age related macular degeneration, retinal disease or detachment, glaucoma, aphakia/pseudophakia, corneal opacities, cataracts, manifest or latent nystagmus.
- Presence of systemic disease (such as diabetes, thyroid, or collagen vascular disease), neurological issues (with the exception of extraocular muscle paresis causing strabismus), Autism, developmental delay, Cerebral Palsy (CP), or Attention Deficit Hyperactivity Disorder (ADHD).
- Lack of consent.

Volunteers Needed for Research

The IWK Health Centre and Dalhousie University are conducting a study exploring how well individuals with amblyopia ("lazy eye") are able to see using a new test called the Manchester Radial Deformation Acuity Chart.

We are currently looking for people with amblyopia "lazy eye" between the ages of 6 and 12 years of age to take part in the study.

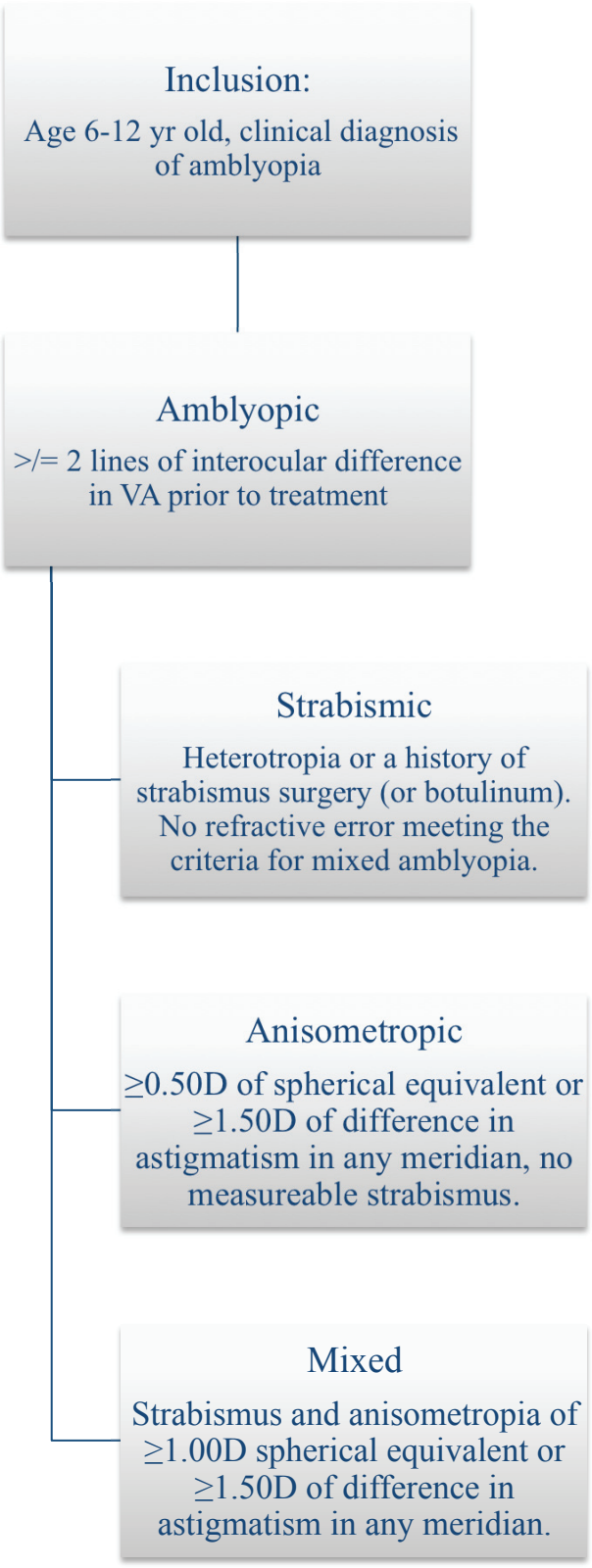
The study will take about 1 hour of your time. If you are interested in participating in this research or would like more information please contact:

Steve Van Iderstine at: 470-2741

Or

Michael Betts at: mjbetts@dal.ca

Appendix H. Study Patient Population



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