ACCOMMODATIVE STABILITY IN THE DEVELOPING VISUAL SYSTEM

By

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OD, MS

DISSERTATION

In partial satisfaction of the requirements for the degree of

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DEDICATION

I dedicate this dissertation to my wife, Carrie, for all her unconditional love and support.

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LIST OF ACRONYMS

Abbreviations	Expansion
D	Diopters
DOF	Depth-of-field
HFC	High frequency component (variability of the accommodative response in the frequency domain)
ICC	Intra-class correlation coefficient
LFC	Low frequency component (variability of the accommodative response in the frequency domain)
MA	Meter angle
RMS	Root mean square (variability of the accommodative response in the time domain)
SD	Standard deviation
SE	Spherical Equivalent
Sw	Within subject standard deviation

GENERAL ABSTRACT

Purpose: The purpose of this work was to gain an understanding of the impact that extrinsic, intrinsic and cognitive factors have on accommodative accuracy (lag) and variability (RMS) in young children with uncorrected hyperopia. Individuals with greater amounts of hyperopia must exert a larger accommodative response to achieve the same level of accommodative accuracy as an individual with a lesser hyperopic refractive error. Given that accommodative responses are positively correlated with RMS, which in turn is positively correlated with depth-of-field (DOF), children with uncorrected hyperopia may experience greater RMS that may also impact their ability to detect blur. Additionally, the accommodative response has been shown to be influenced by the cognitive demand of the viewing task, which may impact the RMS observed in these children. Experiments investigating accommodative accuracy and variability under different viewing conditions were performed on both children with varying amounts of uncorrected hyperopia and adults for comparison with a mature visual system.

Methods: Lag and RMS were measured over 3 experiments using photorefraction in children 3 to <10 years with a range of uncorrected hyperopia (+0.06D to +4.91D spherical equivalent (SE) of the most plus eye) and visually normal uncorrected adults (+0.08D to +1.51D SE). **Experiment 1** investigated the impact blur and disparity cues have on lag and RMS by systematically removing these cues from the stimulus. Relationships between total accommodative response and lag and RMS were investigated. **Experiment 2** measured blur detection thresholds and DOF psychophysically. Associations between blur detection thresholds with independent variables RMS, age, SE and lag and associations between DOF and RMS were investigated. **Experiment 3** investigated the impact of cognitive effort on lag and RMS as functions of SE and the total accommodative response for both passive and active viewing conditions.

Results: Experiment 1) In children, accommodation was most accurate and stable when blur and disparity cues were present in the stimulus. The removal of blur cues from the stimulus resulted in both greater lag and RMS than the removal of disparity cues. In adults, RMS was not impacted by the removal of blur or disparity while lag was significantly greater when blur-cues were removed. **Experiment 2)** In children, increased RMS, increased SE and younger age were significantly associated with increased blur detection thresholds. RMS and age were independently associated with blur detection thresholds when controlling for the other independent variables. Additionally, increased SE was significantly associated with increased RMS when controlling for age and lag. **Experiment 3)** In children, increased cognitive effort resulted in a smaller average accommodative lag and decreased RMS. Increased SE was significantly associated with increased lag and increased RMS in the passive viewing condition only. In adults, cognitive effort did not significantly affect lag, however, a small significant difference in RMS was detected with cognitive effort compared to passive viewing but the difference is unlikely to be clinically meaningful. **Children vs. Adults)** The children had significantly greater DOF and blur detection thresholds and RMS than the adult subjects throughout all experiments.

Conclusions: Children do not have adult-like RMS, which may be secondary to children having larger blur detection thresholds and DOF than adults. Children appear to rely more heavily on both blur and disparity cues for accommodative accuracy and stability than adults. Additionally, cognitive effort appears to improve accommodative accuracy and stability in children more than adults, as measured responses in adults did not

change with cognitive effort. Lastly, the impact of uncorrected hyperopia on lag and RMS was variable across conditions suggesting that while children with uncorrected hyperopia may experience greater lag and RMS at times, their accommodative behavior is not consistently poorer across near tasks.

CHAPTER 1: Introduction

1.1 Introduction

Visual experience depends on both retinal image quality and eye alignment, which are both dependent on oculomotor responses (accommodation and vergence). The oculomotor response is a complex interaction between the afferent and efferent visual systems. The afferent system allows for optimal visual acuity, contrast sensitivity, object perception, motion detection, stereopsis and spatial navigation to occur, whereas the efferent system allows individuals to interpret and interact with the environment through motor output.

Abnormal early visual experience can result in anomalous development of either the afferent or efferent oculomotor systems, or both (Hubel and Wiesel 1965, Hubel and Wiesel 1970, Kiorpes and Boothe 1980, Harwerth, Crawford et al. 1981, Boothe, Kiorpes et al. 1982, Harwerth, Smith et al. 1983, Harwerth, Smith et al. 1997). The abnormal development of the oculomotor system may, in turn, lead to clinical anomalies such as strabismus, amblyopia, suppression, anomalous correspondence, and eccentric fixation. The premise of current treatment for a developmental abnormality of the eye is to redirect the visual experience of the patient by altering their visual system or their environment. Unfortunately, current treatment paradigms are not fully effective (Huang, Tao et al. 2007, Repka, Kraker et al. 2008, Repka, Kraker et al. 2010) and their mechanistic underpinnings are only poorly understood. To more effectively manipulate visual experience and increase the success of treatment of these clinical abnormalities we must understand how the afferent and efferent circuits of the oculomotor system interact to guide typical development.

The ideal approach to understanding the impact of the visual experience of young children would be to record their retinal image quality and eye alignment throughout the day while they complete their daily habitual activities. Unfortunately, this method is not feasible due to the limitations of equipment and the lack of a controlled environment. Therefore, the approach taken in this work was to make targeted measures of visual experience designed to provide new insight about specific clinical questions. For example, many practitioners make the assumption that a school aged child with a moderate amount of uncorrected hyperopia is able to produce sufficient accommodation for near activities and sustain an adequate level of accommodation throughout activities of long durations, such as reading and homework. These assumptions are often based upon clinical measurements of accommodative accuracy over a few seconds of viewing time. Even previous scientific studies of sustained accommodation have not assessed continuous measures of accommodation in typical infants and young children for time intervals of greater than thirty seconds (Candy and Bharadwaj 2007, Schultz, Sinnott et al. 2009, Anderson, Glasser et al. 2010). Currently, accommodative behavior during a sustained near task of the duration more representative of habitual daily near activities is unknown for both typically developing children and children with greater amounts of hyperopia.

Retinal image quality is an important visual function that is often at the forefront of discussions of visual experience as it impacts the development and treatment of amblyopia and strabismus. However, retinal image quality may also be important in individuals without amblyopia and strabismus as poor image quality may impact quality of life (Kollbaum, Jansen et al. 2012). Clinically, the accuracy of accommodation is determined as a measure of defocus and is used to infer retinal image quality. The accuracy of accommodation to a target of regard is often referred to as a stable and discrete measure over time. However, the accommodative response is actually variable and tends to fluctuate around the mean accommodative response. The fluctuations of accommodation about the mean are often referred to as accommodative microfluctuations (Charman and Heron 1988). Accommodative microfluctuations have been described in both the frequency and time domains. In the frequency domain, microfluctuations are described using power spectral analysis and have been shown to have both a low frequency component (LFC) and a high frequency components (HFC) (Charman and Heron 1988). In the time domain, microfluctuations are described using root mean square analysis (RMS) (Day, Strang et al. 2006) and have been shown to have magnitudes of approximately 0.20 to 0.30 D in adults when viewing stimuli at a near distances (25 and 33 cm) (Kotulak and Schor 1986, Seidel, Gray et al. 2005, Yao, Lin et al. 2010).

Accommodative microfluctuations may occur due to “tremor” that may be part of the sensory feedback loop (Campbell, Robson et al. 1959), noise in the accommodative plant (Kotulak and Schor 1986), or as part of the accommodative control mechanism (Campbell, Robson et al. 1959, Kotulak and Schor 1986, Charman and Heron 1988, Abbott, Schmid et al. 1998, Yao, Lin et al. 2010). Many previous studies of accommodative microfluctuations have sought to understand the role of the fluctuations in terms of the accommodative control mechanism (Campbell, Robson et al. 1959, Kotulak and Schor 1986, Charman and Heron 1988, Abbott, Schmid et al. 1998, Yao, Lin et al. 2010). Given that over small time periods (≤20 seconds), accommodative microfluctuations have been shown to be smaller than the depth-of-focus of the eye in cooperative adult subjects, accommodative microfluctuations may act as error detectors to maintain a stable accommodative response (Kotulak and Schor 1986, Yao, Lin et al. 2010). When considering microfluctuations in the role of the accommodative control system, it has been suggested that in the frequency domain, the LFC acts as a sub-threshold error detector for the accommodative control system in adults (Charman and Heron 1988, Winn, Pugh et al. 1990), while the HFC has been found to be correlated with arterial pulse (Winn, Pugh et al. 1990).

While accommodative variability is often referred to in the literature as accommodative microfluctuations, it is important to note that the term ‘accommodative microfluctuations’ should be not automatically be inferred to be representative of the blur detection mechanism of the ocular motor control system, as many studies use the term accommodative microfluctuations to simply describe the variability of the steady-state accommodative response (Campbell, Robson et al. 1959, Denieul 1982, Gray, Winn et al. 1993, Gray, Winn et al. 1993, Niwa and Tokoro 1998, Candy and Bharadwaj 2007, Schultz, Sinnott et al. 2009, Anderson, Glasser et al. 2010). Additionally, it is worth noting that there is an underlying assumption that the stimulus is perceived as being clear and that the individual’s perception of clarity is not changing during the accommodative measures. Thus, while accommodative microfluctuations are assumed to be acting as a blur detector in the ocular motor control system, the term accommodative microfluctuations is a general term used to describe the variability of the accommodative response, regardless of whether the measures are reported in the time or frequency domain or were taken over short or long measurement periods. In this body of work, terms accommodative microfluctuations and accommodative variability are used interchangeably and both represent accommodative variability in both the time (RMS) and frequency (LFC) domains.

While there has been extensive investigation of accommodative microfluctuations, the majority of the research on this topic has been performed on adults (Charman and Heron 1988) and over time periods of less than 30 seconds (Campbell, Robson et al. 1959, Kotulak and Schor 1986, Kotulak and Schor 1986, Gray, Winn et al. 1993, Candy and Bharadwaj 2007, Schultz, Sinnott et al. 2009, Anderson, Glasser et al. 2010). Given that the developing visual system possesses different optical characteristics from the mature adult visual system (Green, Powers et al. 1980, Bradley and Freeman 1982), it is reasonable to assume the behavior of the microfluctuations may differ as well, thereby impacting the quality and stability of the retinal image and visual experience. Children have, on average, higher levels of hyperopia than older children (Zadnik, Manny et al. 2003, Multi-Ethnic Pediatric Eye Disease Study 2010, Wen, Tarczy-Hornoch et al. 2013), and adults (Shufelt, Fraser-Bell et al. 2005), consequently they also have larger accommodative demands for any given viewing distance. Thus, understanding the factors that impact the accuracy and stability of the accommodative response is critical to gain perspective into the visual experience of young uncorrected hyperopes.

Blur is thought of as the primary sensory cue that drives the accommodative response (Heath 1956, Schor 1985, Mays and Gamlin 1995), however, disparity also impacts the accommodative response indirectly through the vergence motor response by what is known as the CAC ratio (Judge and Cumming 1986, Schor 1986, Mays and Gamlin 1995, Hung 1997). Several studies have shown that accommodation is most accurate when blur and disparity cues are available in the stimulus (Turner, Horwood et al. 2002, Bharadwaj and Candy 2008, Horwood and Riddell 2009), however, the impact on accommodative microfluctuations when disparity is removed is less understood. In adults, Campbell et al. (1960) found that accommodative fluctuations decrease when the stimulus is viewed binocularly and disparity cues are available (Campbell, Westheimer et al. 1958) while Seidel et al. (2005) and others found that the magnitude of accommodative microfluctuations did not systematically differ when comparing binocular and monocular viewing conditions (Charman and Heron 1988, Seidel, Gray et al. 2005). The impact of blur and disparity cues on the stability of the accommodative response in the developing visual system of children is unknown.

Accommodative microfluctuations have also have been shown to increase with an increase in the accommodative response in infants (Candy and Bharadwaj 2007), children (Anderson, Glasser et al. 2010), and adults (Kotulak and Schor 1986, Anderson, Glasser et al. 2010). It has been suggested that the increase in variability with an increase in response is likely due to the physical properties of the accommodative plant secondary to the decrease in tension of the lens zonules during accommodation (Kotulak and Schor 1986, Gray, Winn et al. 1993). The potential impact of an increased accommodative response is particularly important in individuals with larger amounts of uncorrected hyperopia as they must generate a larger accommodative response than others with lesser amounts of hyperopia for any given viewing distance. The concern with an increased response is not only in regards to accommodative microfluctuations but also with the vergence system as the two systems impact one another through neural cross-links (Schor 1986, Mays and Gamlin 1995). In object space, the demand for vergence and accommodation are equal when using meter angles (MA) and dioptric units as the inverse of the stimulus distance (Kersten and Legge 1983). Therefore, as individuals fixate stimuli at various target distances, accommodation and vergence are synergistic in that they operate in the same visual direction. For example, as the accommodative demand increases, so does the convergence demand. It is generally thought that it is beneficial for the two systems to be linked and to work in the same visual direction. However, for children with greater amounts of hyperopia, the synergistic relationship could be problematic as a child with greater amount of hyperopia has greater accommodative demand than a child with lesser amount of hyperopia, yet the vergence demand is equal between the different hyperopic children if similar interpupillary distances are assumed.

Thus, the purpose of Chapter 2 was to investigate the stability of the accommodative response in the developing visual system: 1) under binocular, full cue conditions 2) when cues to accommodation are systematically removed from the stimulus by occluding an eye or displaying a target without blur cues and 3) when cues of blur and disparity are uncoupled through the introduction of minus lenses or added base-out prism.

As mentioned above, in adults, in terms of an accommodative control mechanism, accommodative microfluctuations are thought to act as sub-threshold blur detectors. There is a range in dioptric space, known as the depth-of-field (DOF), in which changes in object vergence are not detected by the visual system as an error (Wang and Ciuffreda 2006). Analogous to the DOF, is the depth-of-focus, which represents the amounts of dioptric blur on the retina that is not detected by the visual system as an error. Often times in discussion of the error detector in accommodative control models, DOF is considered to be a dead zone in which changes in object vergence do not elicit the perception of blur (Schor 1985, Jiang 1997). Kotulak and Schor (1986) have investigated accommodative microfluctuations in the context of the depth-of-focus of the eye in adults (Kotulak and Schor 1986). They found that the amplitude of the microfluctuations are smaller than subjective measures of depth-of-focus and suggest that they minimize the perception of blur by acting as a sub-threshold error detector that acts as part of the accommodative controller system to maintain the mean accommodative response without individuals perceiving any change in object clarity (Kotulak and Schor 1986). Kotulak and Schor suggested that blur may be detected by two systems, one of which is regulated by the accommodative controller system to maintain the accommodative response and the other which is regulated by higher order neurological systems where blur is perceived by the individual (Kotulak and Schor 1986). Yao et al (2010) investigated microfluctuations in terms of their association between what the authors termed the objective depth-of-focus (changes in accommodation without a change in target clarity, similar to Kotulak and Schor's accommodative controller system model) and subjective depth-of-focus (perceived change in target clarity; similar to Kotulak and Schor's higher order neurological control system for the perception of blur) (Yao, Lin et al. 2010). Similar to Kotulak and Schor (1986), Yao et al (2010) found that the objective depth-of-focus was less than the subjective depth-of-focus and that accommodative microfluctuations were correlated with an individual's objective depth-of-focus. Yao et al (2010) also found that the magnitude of the objective depth-of-focus increased with an increase in accommodative demand, which again, was positively correlated with the microfluctuations. Anderson et al. (2010) found that children have larger microfluctuations than adults, suggesting that perhaps they also have larger blur thresholds than adults (Anderson, Glasser et al. 2010). Additionally, because children have, on average, larger amounts of hyperopia than adults (Zadnik, Manny et al. 2003, Shufelt, Fraser-Bell et al. 2005, Multi-Ethnic Pediatric Eye Disease Study 2010, Wen, Tarczy-Hornoch et al. 2013), they would have, on average, larger accommodative demands if left uncorrected, which may be associated with larger microfluctuations.

Thus, the purpose of the experiments in Chapter 3 was to determine if there was an association between accommodative microfluctuations and blur detection thresholds in children under full-cue binocular viewing conditions. An additional purpose of the experiments in Chapter 3 was to determine if the children had higher blur detection thresholds or larger DOF than the adults, which may explain why children have been found to have larger accommodative microfluctuations (Anderson, Glasser et al. 2010).

Currently the stability of the accommodative response in children beyond a 30 second period is unknown. Accommodative stability may be of particular concern during the school day while performing near activities and while completing homework outside of school (Cotter 2007). Additionally, little is known about the effect of hyperopic refractive error on accommodative stability. Again, based on previous studies demonstrating that accommodative microfluctuations increase with increasing accommodative demands (Miege and Denieul 1988, Candy and Bharadwaj 2007, Anderson, Glasser et al. 2010), one could expect individuals with uncorrected hyperopia to have increased microfluctuations relative to similar aged children with emmetropia, which may become more pronounced with a longer viewing time due to fatigue.

The literature also suggests the accommodative response is influenced by neural and cognitive factors in addition to optical and stimulus characteristics. Schor, et al. (1992)

found the sense of nearness, or proximal effect, can alter the accommodative response (Schor, Alexander et al. 1992). Others have found that by increasing the cognitive demand of a task, the accommodative response increases and therefore the lag is reduced (Bullimore and Gilmartin 1988, Woodhouse, Cregg et al. 2000, Francis, Jiang et al. 2003). As the accommodative lag decreases, the overall accommodative response increases, which may in turn affect the accommodative microfluctuations. However, the effect of increased cognitive effort on accommodative microfluctuations has not yet been studied.

The purpose of Chapter 4 was to investigate accommodative accuracy and variability during a passive viewing task versus an active viewing task, each 10 minutes in duration. Accommodative accuracy and variability were compared between the passive and active viewing conditions. Additionally, changes in accommodative accuracy and variability were analyzed over time to determine if subjects with greater amounts of hyperopia experienced more changes in accommodation over time than subjects with lesser amounts of hyperopia.

Typically developing children between the ages of 3 and < 10 years were recruited to represent different stages of the developing visual system for the experiments in the subsequent chapters. The children recruited for the study had a large range of uncorrected hyperopia (+0.08 to +4.91 diopters (D) most plus cycloplegic spherical equivalent), representing various accommodative demands. All recruited subjects were asked to participate in all experiments described in the subsequent chapters, however, not all subjects could or did participate in all experiments. Subject characteristics (age, refractive error and visual acuity) and participation by experimental conditions is summarized in Appendix B. The chosen ranges of age, uncorrected hyperopic refractive error and their associated accommodative demands provided an opportunity to further the understanding of how factors such as accommodative cues, blur detection, cognitive demand, and time affects the accommodative behavior in the developing visual system. Adult subjects were also recruited to act as control subjects with a mature visual system.

CHAPTER 2: The Impact of Visual Cues on the Stability of the Accommodative Response in Children with Uncorrected Hyperopia

2.1 Introduction

The accommodative response in children with uncorrected hyperopia is of interest due to the implication that inaccurate accommodation may result in decreased retinal image quality, and thus may lead to anomalous visual disorders such as amblyopia and strabismus (Ingram, Arnold et al. 1990, Ingram, Gill et al. 1994, Ingram, Gill et al. 2000, Fawcett and Birch 2003). The accommodative response itself is a product of the interactions between sensory detection of the afferent visual system and motor output of the efferent visual system (Schor, Alexander et al. 1992, Mays and Gamlin 1995, Schor 1999). Blur is often thought of as the sensory visual cue that drives the motor accommodative response (Heath 1956, Schor 1985, Mays and Gamlin 1995), however, disparity cues have also been shown to drive the accommodative response (Schor 1985, Judge and Cumming 1986, Mays and Gamlin 1995, Hung 1997). Several studies have shown that accommodation is most accurate when disparity cues are available during binocular viewing by demonstrating a decrease in the accommodative response when disparity cues are removed from the stimulus during monocular viewing conditions despite the availability of the remaining blur cues (Turner, Horwood et al. 2002, Bharadwaj and Candy 2008, Horwood and Riddell 2009, Horwood and Riddell 2013).

The accommodative response is often discussed in the context of accommodative accuracy, implying that accommodation is static. However, when measured over short time scales (< 30 seconds), accommodation has been shown to be dynamic and oscillate around a mean response at a frequency less than 3 Hz (Campbell, Westheimer et al. 1958, Charman and Heron 1988). The oscillations are referred to as accommodative microfluctuations and can be measured in both time and frequency domains. Accommodative microfluctuations (i.e.: accommodative variability) are also important in the context of image quality, given that an increase in the variability outside of the DOF is likely to result in decreased retinal image quality.

There are many contributing factors that influence the magnitude of accommodative microfluctuations, some of which come from intrinsic properties of the optical system itself while others originate from extrinsic properties of the stimulus and visual environment. A decrease in pupil size (Campbell, Robson et al. 1959, Gray, Winn et al. 1993) and an increase in the accommodative response (Denieul 1982, Kotulak and Schor 1986, Charman and Heron 1988, Anderson, Glasser et al. 2010) have been shown to result in increased accommodative microfluctuations. Accommodative microfluctuations have also been shown to increase as luminance and image contrast decrease (Schor, Johnson et al. 1984, Charman and Heron 1988). Other studies have found that an increase in the accommodative response is associated with an increase in accommodative variability, which is thought to be secondary to noise of the accommodative plant (Kotulak and Schor 1986). Another factor that may influence accommodative microfluctuations is whether the stimulus is viewed binocularly when disparity cues are present, or monocularly when disparity cues are removed but blur cues remain. The effect disparity cues have on accommodative microfluctuations is currently up for debate as Campbell and Westheimer (1960) found that accommodative microfluctuations decreased under binocular viewing (Campbell and Westheimer 1960) while other studies have shown that viewing a stimulus monocularly in the absence of disparity cues does not systemically affect accommodative variability despite the observed decrease in accommodative response (increase in accommodative inaccuracy) under monocular viewing conditions (Charman and Heron 1988, Seidel, Gray et al. 2005).

In addition to a lack of agreement regarding the effect of disparity on the stability of the accommodative response when blur cues are present, it is also unknown how the stability of the response is affected when blur and disparity cues are uncoupled. Typically, in object space, the demand for vergence and accommodation are equal using MA and dioptric units as the inverse of the stimulus distance (Kersten and Legge 1983). Consequently as individuals fixate stimuli at various target distances, accommodation and vergence typically operate in the same visual direction. For example, as the accommodative demand increases, so does the convergence demand. It has been shown that when the visual cues are manipulated such that the responding vergence and accommodative systems have to work in opposite directions due to decoupling of visual cues (through the use of prism or lenses), some individuals do not make an appropriate vergence response while others do not make an appropriate accommodative response (Bharadwaj and Candy 2009). It is unknown, however, what effect uncoupled cues have on the stability of the accommodative response, which may be particularly important for the young uncorrected hyperope since they have similar vergence demands as age matched peers with similar interpupillary distances, but have greater accommodative demands due to uncorrected hyperopia.

Despite numerous previous investigations of the impact of various visual cues on accommodative microfluctuations, these past studies have all been conducted on adult subjects and thus little is known about the impact of visual cues, such as blur or disparity, on accommodative microfluctuations in the developing visual system. Young children with uncorrected hyperopia are of particular interest given that they have larger accommodative demands than their emmetropic peers and may be susceptible to increased microfluctuations when they accommodate to compensate for their hyperopic defocus. Additionally, because children with larger amounts of hyperopia have greater amounts of defocus to overcome, it is important to understand the relative role of blur cues on the overall response.

The purpose of this study was to investigate the total accommodative response and accommodative microfluctuations in the presence and absence of blur and disparity cues in emmetropic and uncorrected hyperopic children aged 3 to < 10 years with adult subjects used as controls to represent a mature visual system.

2.2 Methods

2.2.1 Study Subjects

Subjects aged 3 to < 10 years and non-presbyopic adult subjects were recruited from the University of Houston College of Optometry staff, student, and patient populations, as well as the local community. The study followed the tenets of the Declaration of Helsinki and was approved by the University's institutional review board for the protection of human subjects. All subjects over the age of 18 years provided written informed consent and subjects younger than 18 years provided assent while their parents provided written parental permission to participate in the study.

Prior to participation in the study, subjects or their parents (in the case of child participants) were queried to ensure subjects met the inclusion criteria of ≥ 32 weeks gestation and a birth weight ≥ 2500 grams. Subjects were also screened for the presence of exclusion criteria: history of ocular or systemic diagnoses that may impact accommodation, were taking medications known to impact accommodation, or had a history of developmental delays or behavioral diagnoses, such as attention deficit disorders. Subjects were also ineligible from participation if they had a current or previous refractive error correction or had known cycloplegic refractive error ≤-0.50 diopters (D) spherical equivalent (SE), anisometropia > 1.00 D SE or astigmatism > 1.25 D cylinder.

In addition to participating in the experiment, all subjects had a complete vision examination performed by the investigator. The vision examination included monocular visual acuity with isolated letters surrounded by crowding bars (top, bottom, left and right positioned at one letter width from the letter) following the electronic psychometric visual acuity testing protocol established by the Pediatric Eye Disease Investigator Group (electronic HOTV (Holmes, Beck et al. 2001, Moke, Turpin et al. 2001) for subjects < 8 years and ETDRS (Beck, Moke et al. 2003) for subjects ≥ 8 years presented on the M&S SmartSystem (M&S Technologies, Inc. Niles, IL) calibrated for testing at 14.5 feet. In addition to visual acuity testing, unilateral cover test was performed to rule-out strabismus. Subjects were excluded from data analysis if they did not have typical visual acuity for their age (<20/50 for 3 to < 4 years, <20/40 for 4 to < 5 years, <20/32 for 5 to < 6 years (Pan, Tarczy-Hornoch et al. 2009), 20/25 or worse for subjects ≥ 6 years (Scheiman, Hertle et al. 2008) or were diagnosed with strabismus (any movement seen on unilateral cover test) or amblyopia (visual acuity > 2 lines intraocular difference) (Pediatric Eye Disease Investigator 2002).

Subjects also had a cycloplegic assessment of refractive error using the Grand Seiko WAM-5500® open-field auto-refractor (RyuSyo Industrial Co., Ltd. Hiroshima, Japan), and a dilated fundus examination to rule out ocular pathology. Three measures of cycloplegic refractive error were obtained for each eye (30 minutes after instillation of 1% cyclopentolate). Each of the three measures were transformed into power vector notation, which represents the original sphero-cylinder refractive error as three powered lenses: a spherical lens power M (i.e.: spherical equivalent), and two Jackson Cross Cylinder lenses, one with power J_0 at axis 0° and the other with power J_{45} at axis 45° (Thibos, Wheeler et al. 1997). Once each of the cycloplegic measures were transformed into power vector notation, the three respective values for each vector were averaged, then the three average vectors were back-transformed to represent the mean sphero-cylinder cycloplegic refractive error for the right and left eye of each subject.

Power refraction was the technique used to dynamically record accommodative responses during experimental conditions and only provides measures of refraction in the vertical meridian (described in further detail below and in Appendix A). Thus, the back-transformed mean refractive error from cycloplegic autorefraction in sphero-cylinder form was used to calculate the power in the vertical meridian (090) of the eye (described below) in order to combine the cycloplegic auto-refraction and power refraction measures within each subject to calculate the total accommodative response of the subject (described in detail in the data analysis section).

The vertical meridian of each eye, as measured by auto-refraction, was calculated as follows:

$$Power\ in\ Vertical\ Meridian = S + Csin^2(90 - \alpha)$$

where *S* is the spherical power, *C* is the cylindrical power, *α* is the axis, and *90* represents the desired vertical meridian.

For children who were recruited from the optometry clinic, eligibility was known prior to the consent process, as the clinicians who referred the patient to the study were aware of the study inclusion/exclusion criteria. Children recruited outside of the optometry clinic were queried and screened for the exclusion criteria regarding previous diagnoses and medications and any history of spectacle correction prior to the laboratory visit, however, the refractive error exclusion criteria and other vision examination criteria were determined at the vision examination, which occurred after the laboratory visit. Children identified during the vision examination to be ineligible were not included in the analysis.

2.2.2 Experimental Conditions

To determine the relative importance of blur and disparity cues on the accommodative response, subjects viewed the stimuli under the following 3 viewing conditions at both 100 and 33 cm:

- Blur+disparity: Binocular viewing of high contrast stimulus. Blur and disparity cues were both closed-loop.
- Blur-only: Monocular viewing of high contrast stimulus to eliminate disparity cues while blur cues were preserved. The accommodation system was closed-loop while vergence system was open-loop.
- Disparity-only: Binocular viewing of a difference of Gaussian (DOG) stimulus (described below) which contained only low spatial frequency information to eliminate blur cues while disparity cues were preserved. The vergence system was closed-loop while the accommodation system was open-loop.

Additionally, the terms blur-only and disparity-only are in reference to one another. For example, the blur-only condition does not have disparity cues available while the disparity-only condition does not have blur cues available. However, other cues, such as proximal cues, remain in the stimulus.)

To determine the relative importance of accommodation and vergence functioning in the same visual direction, subjects viewed the stimuli while blur and disparity cues were uncoupled using minus lenses and base-out prism as follows (Bharadwaj and Candy 2009):

- Lens-induced uncoupled cues: Binocular viewing through -2.00 D lenses in front of each eye at 100 cm.
- Prism-induced uncoupled cues: Binocular viewing through 2 meter angle (MA) base-out prism scaled by each individual subject's inter-pupillary distance with the total prism amount split between the two eyes at 33 cm.

The lens uncoupled condition was performed at 100 cm to maintain a similar accommodative demand for each experimental trial.

To ensure there were no effects of stimulus presentation order on the results, all testing conditions were presented in a pre-determined randomized order specific to each subject.

2.2.3 Stimuli Presentation

The stimuli were displayed on an iPad Air® (Apple Inc., Cupertino, CA) (2048 x 1536 pixels) using Keynote® (Apple Inc., Cupertino, CA) presentation software within a total stimulus viewing area of 4.15 cm (7.20º) horizontally and 2.2 cm (3.8º) vertically. The iPad Air® was mounted above a beam-splitter (passes infrared light, reflects visible light), and positioned to create either a 33 cm or 100 cm viewing distance for the subject in primary gaze.

Prior to testing, subjects aged 6 to < 10 years were administered The San Diego Quick Assessment (La Pray M. 1969) test as a screening assessment to estimate each child's individual reading level. Children who were unable to correctly read aloud 9/10 words from the lowest level of the assessment (pre-primer) were shown the shapes, otherwise the children aged 6 to < 10 years were shown the Sloan letters. All children < 6 years were shown the shapes, irrespective of their reading ability.

Both shapes and words were scaled for each viewing distance such that they subtended 0.21° in the vertical dimension (for the letter stimuli the size was based on lower case letters such "a" and "s") at 99.7% Weber contrast through the beam splitter (stimulus: 0.02 cd/m^2; background: 5.97 cd/m^2). Words or shapes were presented in the center of the stimulus window one at time, switching every 2 seconds, with a total duration of one minute per experimental condition. The subjects viewed the stimulus binocularly for the blur+disparity, lens-induced and prism-induced uncoupled cue conditions. For the blur-only experiment, the subjects viewed the stimulus with their right eye while their left eye was occluded using a Kodak 89B Wratten gelatin filter that blocks visible light while transmitting infrared light, allowing the PowerRef II (PR) (Plusoptix Inc., Atlanta, GA) to obtain refractive error measures of the occluded eye (measures of the right eye were used for data analysis purposes and measures of the occluded eye were used for data exclusion criteria only as described below). By viewing the stimulus monocularly, vergence was open-loop while accommodation remained closed-loop. For the disparity-only condition, subjects viewed a “differences of Gaussian” (DOG) stimulus (Figure 2.1) binocularly. The DOG stimulus minimizes blur cues while preserving disparity cues, allowing accommodation to be open-loop while vergence remains closed-loop (Kotulak and Schor 1987). The DOG stimulus was generated by calculating the difference between a broad Gaussian and a narrow Gaussian using the following equation,

$$DOG(x) = 3e^{\left(\frac{-x^2}{\sigma^2}\right)} - 2e^{\left(\frac{-x^2}{2.25\sigma^2}\right)} + 1$$

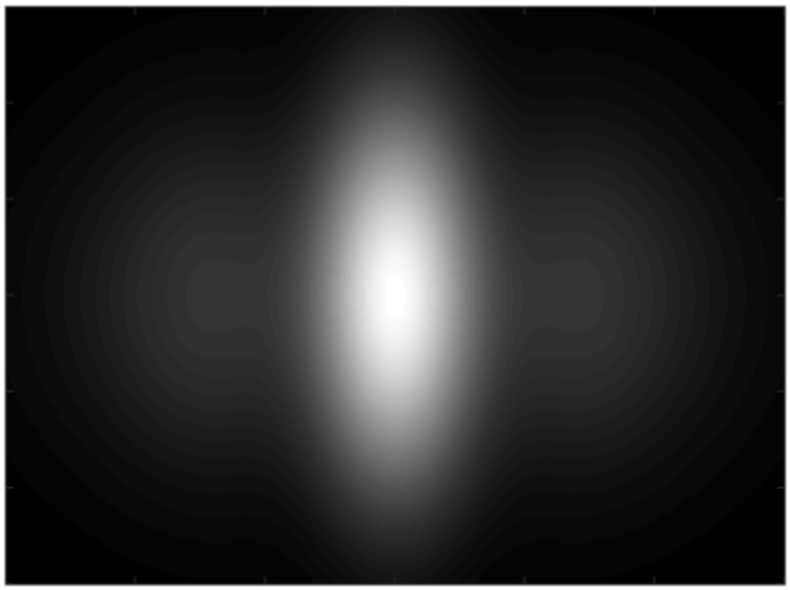
where *x* represents the position in space in the horizontal direction (degrees) and *σ* represents the space constant (1.6 degrees). Next, the DOG was multiplied by a third luminance Gaussian to minimize edges around the border of the stimulus to further minimize the stimulus to accommodation (Tondel and Candy 2008) as follows:

$$Luminance(x) = e^{\left(\frac{-p^2}{20}\right)}$$

where *p* represents the distance from the center to the border of the stimulus. The center of the DOG stimulus had a luminance of 3.5 cd/m^2. To further ensure blur cues were not visible in the stimulus, the subjects wore Rollens wraparound sunglasses (Rollens, Parker, CO) during the disparity-only condition. To ensure the DOG stimulus did not provide blur cues that would elicit an accommodative response, the 10 adult subjects who participated in the study also viewed the DOG stimulus monocularly with the right eye while a -2.00 D lens was placed in front of the right eye for 3 seconds then removed. The procedure was repeated 5 times. The adult subjects did not elicit an accommodative response to the minus lenses suggesting the DOG stimulus did not provide adequate blur cues to drive the accommodative response.

The stimulus apparatus as well as the PR were covered using a curtain enclosure throughout the experimental testing condition and the room lights were dimmed to limit any distractions and aid in photorefraction measurement capture. The subjects were positioned in a headrest throughout the experiments to limit head movements. Subjects were instructed to look at the stimuli for each experimental trial and if the subjects looked away, they were reminded and encouraged to fixate stimulus.

Figure 2.1 Differences of Gaussian (DOG) stimulus used to minimize blur cues in the disparity-only viewing condition.



2.2.4 Measures of Refractive Error, Eye Position and Pupil Size

Changes in refractive error in the vertical meridian of the eye, eye alignment and pupil size were measured in all experimental conditions using the PR. The method of eccentric photorefraction has been described in detail elsewhere (Schaeffel, Wilhelm et al. 1993, Gekeler, Schaeffel et al. 1997, Choi, Weiss et al. 2000) and in Appendix A. Prior to experimental testing, each individual underwent a trial lens calibration for each eye to obtain more precise measures of refractive error, described in detail in Appendix A.

Photorefraction data were filtered offline to eliminate outlying data points that are known to be outside of the working range of the PR or points that are unlikely to be physiological in nature (i.e.: large fluctuations secondary to a blink). Measures of refractive error were removed if the change in focus between two data points were > 10D/second (Harb, Thorn et al. 2006), refractive error measures were < -6.00 D or > +4.00 D (Gekeler, Schaeffel et al. 1997, Choi, Weiss et al. 2000), pupil size was < 4 mm or >8 mm (Choi, Weiss et al. 2000), and gaze position was outside of ± 10° horizontally or ± 5° vertically to eliminate erroneous measures from peripheral refraction (Jennings and Charman 1981, Navarro, Artal et al. 1993, Choi, Weiss et al. 2000).

2.2.5 Data Analysis

The relationship between accommodative variability and the total accommodative response was evaluated for each of the experimental conditions. The total amount of accommodative variability for each one-minute trial was characterized in the time domain using root mean square (RMS) calculated from the calibrated refractive error measures obtained by the PR from the right eye of all subjects. The total accommodative response was calculated as the difference between the cycloplegic refractive error in the vertical meridian of the right eye obtained from Grand Seiko auto-refraction and the refractive error measures obtained by the PR during all experimental conditions (PR measures the vertical meridian of the eye in dynamic mode). For the lens-induced uncoupled condition, an additional 2.00 D was added to the total accommodative response value to account for the additional 2.00 D of accommodative demand imposed by the lenses. If the subject's conjugate point of the eye is nearer than infinity, the refractive error obtained by the PR has a negative value. For example, if cycloplegic refractive error in the vertical meridian of the eye was +2.50 D and the refractive error measured during the task was -2.00 D, the total accommodative response would be 4.50 D (the total accommodative response of the lens-induced uncoupled condition would be 6.50 D). Accommodative lag was calculated as the difference between the mean refractive error measures obtained by the PR and the stimulus demand (1 and 3 D for the 100 cm and 33 cm stimulus demands).

The accommodative data were analyzed to determine how RMS was impacted by visual cues in both group and individual analyses. The impact on RMS was considered under three contexts:

1. Increased accommodative response
2. Systematic removal of blur and disparity
3. Blur and disparity under uncoupled conditions

Changes in the accommodative response and RMS secondary to an increased accommodative demand while visual cues remained coupled were evaluated by comparing both the outcomes between the 100 and 33 cm stimulus in children and adults for the blur+disparity, blur-only and disparity-only conditions using paired t-tests with Bonferroni adjustment for multiple comparisons. Next, two-factor (age, condition) repeated measures analyses of variance were performed for each of the outcome variables (total accommodative response and RMS) to determine the mean differences across age (children vs. adults) and condition (blur+disparity, blur-only, disparity-only). Regression analyses (both unadjusted and adjusted for age in the children) were then performed to determine the relationship between the outcome variables (RMS and the total accommodative response) within each condition in both the children and the adults.

Two-factor repeated measures ANOVA was also performed to evaluate the difference in outcomes for the total accommodative response and RMS across age (children vs. adults) and condition in which the cues were uncoupled but the accommodative demand was equal across conditions (lens-induced uncoupled cues and prism-induced uncoupled cues).

Post-hoc analyses for the repeated measures ANOVA testing were conducted using the Holm-Sidek test. For all analyses that included both children and adults, the analyses for the children were completed twice: first using all children and second using only children with refractive errors similar to that of the adults in an effort to isolate differences of the results between age and refractive error. Pearson's correlations were also calculated between RMS and pupil size for each condition to determine if pupil size was related to accommodative variability. All statistical analyses were performed using Stata version 12.1 (StataCorp 2015) and SigmaPlot 13.0 (Systat Software, San Jose, CA) with 2-sided statistical tests at a 0.05 significance level.

2.3 Results

Of the seventy-six subjects recruited to participate in the study (66 children and 10 adults), a total of 58 children and 10 adults were included in the analyses. Of the sixty-six children recruited, eight were excluded from data analysis (3 did not have cycloplegic refractive error measures; 1 did not have a valid calibration for her most plus SE eye; 2 had amblyopia, 1 had astigmatism > 1.25 D, and 1 was born < 32 weeks gestation). Despite 58 children being included in the analysis, not all children completed all experimental conditions (detailed summary of subject participation is found in Appendix B). Summary data for age, cycloplegic spherical equivalent refractive error and cycloplegic refractive error in the vertical meridian of the right eyes for all subjects who participated in the experiment are found in Table 2.1. The means and standard deviations for the total accommodative response, RMS and pupil size (discussed below) measured at 100 cm for the blur+disparity, blur-only, disparity-only, lens-induced uncoupled condition and at 33 cm for the blur+disparity, blur-only, disparity-only, and prism-induced uncoupled experiment are presented in Table 2.2.

TABLE 2.1 Summary statistics for age (years) and cycloplegic spherical equivalent (SE) and cycloplegic refractive error in the vertical meridian (labeled vert merid in table) of the right eye (D) for all children, children with ≤ 1.15 D SE refractive error and adults.

Descriptive Statistics for Subject Characteristics				
		Mean ± SD	**Min**	**Max**
Children (*n* = 58)	Age (yr)	5.9±1.7	3.1	9.9
	SE (D)	+1.41±1.09	-0.37	+4.91
	Vert Merid (D)	+1.33±1.04	-0.26	+4.66
Children ≤ 1.15 D SE (*n* = 28)	Age (yr)	6.6±1.7	3.7	9.9
	SE (D)	+0.61±0.40	-0.37	+1.15
	Vert Merid (D)	+0.55±0.37	-0.26	+1.13
Adults (*n* = 10)	Age (yr)	25.3±2.4	23.3	31.6
	SE (D)	+0.69±0.31	0.08	1.15
	Vert Merid (D)	+0.67±0.35	0.06	1.21

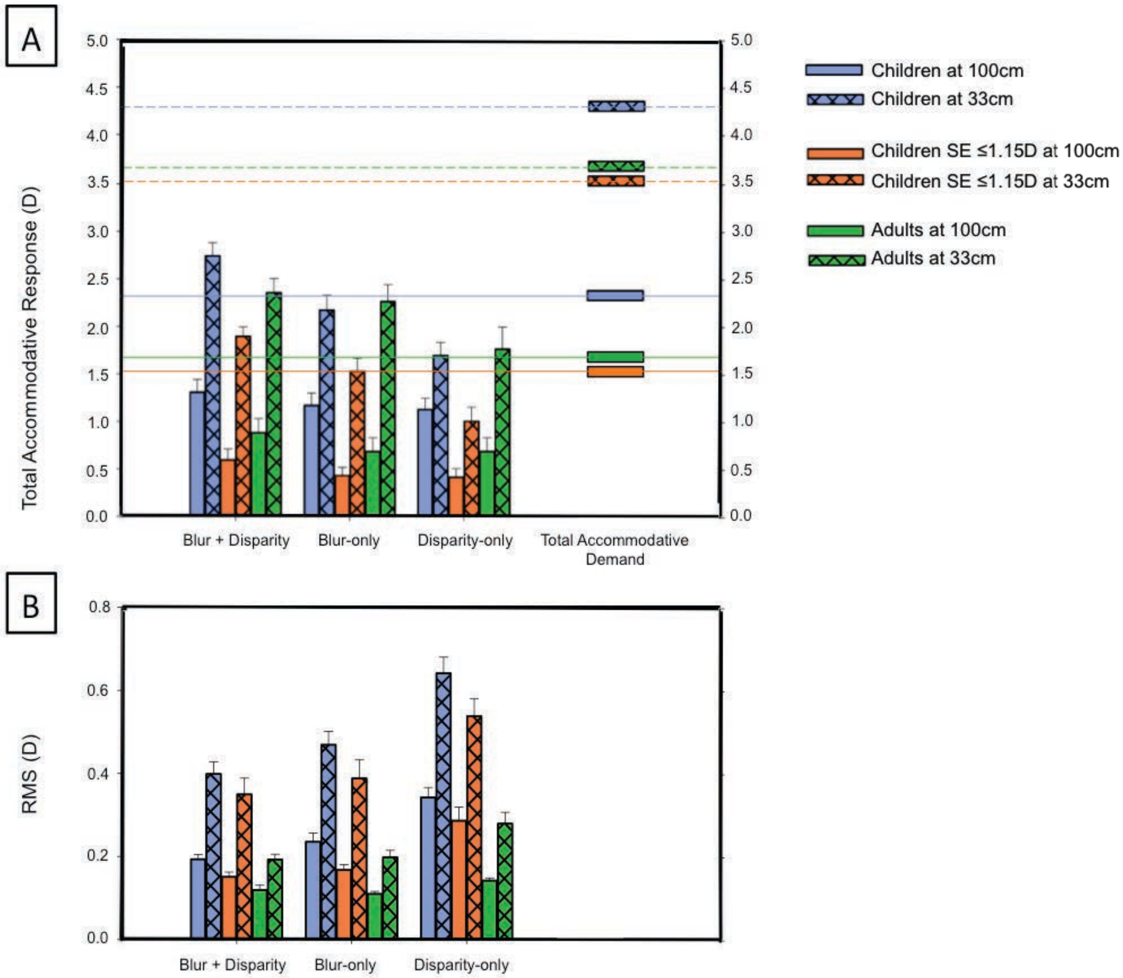
TABLE 2.2 Summary values for all children, children with matched upper limit of hyperopia as compared to the adults (≤ 1.15 D cycloplegic spherical equivalent), and adults for the blur+disparity, blur-only, and disparity-only conditions at 33 cm and the lens-induced uncoupling at 100 cm and prism-induced uncoupling. (Note: The total accommodative response was calculated per individual as the difference between the cycloplegic refractive error in the vertical meridian in the right eye calculated by measures obtained by Grand Seiko auto-refraction and the refractive error measures obtained by the PR during the experiment.)

			Blur+disparity	Blur-only	Disparity-only	Lens-induced	Prism-induced
All Children		*n*	58	58	57	50	57
	Total Accommodative Response (D)	100 cm	1.31±1.04	1.17+1.02	1.12+0.93	1.95±1.17	--
		33 cm	2.74±1.07	2.17±1.20	1.69±1.03	--	3.22±1.10
	RMS (D)	100 cm	0.19±0.09	0.24±0.16	0.34±0.18	0.46±0.21	--
		33 cm	0.40±0.22	0.47±0.24	0.64±0.29	--	0.50±0.27
	Pupil size (mm)	100 cm	6.5±0.6	6.7±0.6	6.7±0.6	6.01±0.5	--
		33 cm	6.2±0.7	6.5±0.6	6.5±0.6	--	5.9±0.7
Children (≤ 1.15 D SE)		*n*	28	28	27	25	27
	Total Accommodative Response (D)	100 cm	0.60±0.60	0.43±0.46	0.41±0.49	1.33±0.64	--
		33 cm	1.90±0.54	1.53±0.74	1.00±0.77	--	2.45±0.68
	RMS (D)	100 cm	0.15±0.06	0.17±0.07	0.29±0.17	0.40±0.19	--
		33 cm	0.35±0.21	0.39±0.24	0.54±0.22	--	0.42±0.25
	Pupil size (mm)	100 cm	6.6±0.5	6.8±0.5	6.8±0.5	6.1±0.5	--
		33 cm	6.2±0.7	6.6±0.6	6.6±0.6	--	6.5±0.6
Adults		*n*	10	10	10	10	9
	Total Accommodative Response (D)	100 cm	0.88±0.47	0.68±0.46	0.68+0.46	1.98±0.71	--
		33 cm	2.36±0.47	2.26±0.57	1.76±0.73	--	2.66±0.74
	RMS (D)	100 cm	0.12±0.04	0.11±0.02	0.14±0.02	0.29±0.07	--
		33 cm	0.19±0.04	0.20±0.05	0.28±0.09	--	0.29±0.22
	Pupil size (mm)	100 cm	6.1±0.7	6.5±0.6	6.7±0.5	5.4±0.6	--
		33 cm	5.0±0.5	5.9±0.7	5.8±0.7	--	5.0±0.6

2.3.1 Changes in Total Accommodative Response and RMS with Increased Accommodative Demand

Measures of accommodation were obtained at 100 cm (1 D demand) to serve as baseline measures for intra-subject comparisons for the increase in demand at 33 cm (3 D demand). The total accommodative response and RMS were compared between the 100 and 33 cm testing distances using paired t-test with Bonferroni correction. The mean total accommodative response and mean RMS values were significantly higher ($p < 0.017$) at the 33 cm testing distance than the 100 cm testing distance for the blur+disparity, blur-only and disparity-only testing conditions in all children, children with matched refractive error to adults, and adults as shown in Figures 2.2a and 2.2b.

FIGURE 2.2 Mean total accommodative response (a) and RMS (b) in children and adults for the blur+disparity, blur-only, and disparity-only conditions at 100 and 33 cm. The mean total accommodative response and mean RMS values were significantly higher ($p < 0.002$) at the 33 cm testing distance than the 100 cm testing distance for the blur+disparity, blur-only and disparity-only testing conditions in all children, children ≤1.15 D SE refractive error, and adults. (Note: The total accommodative response was calculated per individual as the difference between the cycloplegic refractive error in the vertical meridian as calculated by measures obtained by Grand Seiko auto-refraction and the refractive error measures obtained by the PR during the experiment. The mean total accommodative demand for all children, children with ≤1.15 D SE, and adults for 100 cm and 33 cm is shown in the last column of data in the top graph for reference. Thus, the mean accommodative lag is the difference between the representative bar for each condition and the corresponding data line for the total accommodative demand. Additionally, the terms blur-only and disparity-only are in reference to one another. For example, the blur-only condition does not have disparity cues available while the disparity-only condition does not have blur cues available; however, other cues, such as proximal cues, remain in the stimulus.)


A
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
Total Accommodative Response (D)
Blur + Disparity
Blur-only
Disparity-only
Total Accommodative Demand
Children at 100cm
Children at 33cm
Children SE ≤1.15D at 100cm
Children SE ≤1.15D at 33cm
Adults at 100cm
Adults at 33cm
B
0.8
0.6
0.4
0.2
0.0
RMS (D)
Blur + Disparity
Blur-only
Disparity-only

2.3.2 Comparisons Of Total Accommodative Response And RMS Between Children And Adults Across Cue Conditions At 33 cm

Two-factor repeated measures ANOVA with post hoc analysis were performed to determine if there were differences in mean total responses and mean RMS values using age (children and adults) and condition (blur + disparity, blur-only, disparity-only) as factors. The results are found in Table 2.3. The mean total accommodative response for all children at 33 cm was significantly higher in the blur+disparity viewing condition than both the blur-only condition ($p < 0.001$) and disparity-only ($p < 0.001$) conditions. The total accommodative response was also significantly larger ($p < 0.001$) in the blur-only condition as compared to the disparity-only viewing condition. RMS was significantly less in the blur+disparity condition compared to the blur-only ($p = 0.019$) and disparity-only ($p < 0.001$) conditions despite the total accommodative response being highest in the blur+disparity condition. RMS was significantly less in the monocular blur-only condition ($p < 0.001$) than when the stimulus was viewed binocularly in the disparity-only condition even though the total accommodative response was significantly less in the disparity-only condition.

In the adults, the mean total accommodative response was significantly higher ($p = 0.028$) in the blur+disparity viewing condition compared to the disparity-only condition. A significant difference was not detected between the blur+disparity and blur-only conditions ($p = 0.675$), or between the blur-only and disparity-only conditions ($p = 0.056$), though the latter comparison approached significance. A significant difference in RMS was not detected ($p > 0.506$) in any of the comparisons between the blur+disparity, blur-only and disparity-only conditions in the adults.

When comparing all children to adults, a significant difference in the total accommodative response was not detected in any of the comparisons between blur+disparity, blur-only and disparity-only conditions ($p > 0.251$). However, it is important to note that the total accommodative response takes into account the cycloplegic refraction of the subjects (in the vertical meridian), which differed between children and adults (mean +1.33 ± 1.04 D vs. +0.67 ± 0.35 D, $p < 0.001$ unpaired t-test). Thus a similar total accommodative response between groups is indicative of a less accurate accommodative response to the stimulus at 33 cm in children compared to adults since the children had higher average uncorrected refractive error to overcome than the adults. For example, if both a child with +2.00 D SE and an emmetropic adult (plano) had a total accommodative response of 3 D while viewing a stimulus at 3 D (33 cm), the child would have a 2.00 D lag of accommodation whereas the adult would be focused at the target.

To explore the impact that the differences in refractive error between the two groups might have on the total accommodative response between children and adults, a repeated measures ANOVA was performed comparing adults to a subgroup of children with refractive error ≤ +1.15 D SE, the upper limit of the adults. When comparing children and adults with similar upper limit refractive error, a significant difference in total accommodative response was not detected in the blur+disparity condition ($p = 0.060$), although it was approaching significance. The adults did however, have significantly larger total accommodative responses in the blur-only condition ($p = 0.004$) and the disparity-only condition ($p = 0.003$) when compared to children with matched upper limit refractive error.

All children combined had significantly higher RMS values in the blur+disparity ($p = 0.010$), blur-only ($p < 0.001$) and disparity-only ($p < 0.001$) conditions when compared to adults. These findings demonstrate a difference in RMS between children and adults with matched accommodative response, but not matched accommodative accuracy (perhaps leading to differences in defocus of the retinal image). This issue will be addressed in greater detail in Chapter 3. To reduce the likelihood that the differences noted in the RMS response between children and adults were influenced by differences in refractive error, the repeated measures ANOVA was performed with the subset of children with refractive error ≤ +1.15 D SE, the upper limit of the adults. RMS remained significantly larger in this subset of children than adults for the blur+disparity ($p = 0.022$), blur-only ($p = 0.007$), and disparity-only ($p < 0.001$) conditions.

Additionally, intra-condition comparisons were made for the children with ≤ 1.15 D SE for both total accommodative response and RMS. The results are found in Table 2.3. It is evident, that despite including only children with lesser amounts of SE RE, the overall trends of the accommodative behavior remain the same, suggesting that the children's accommodative behaviors were not due to them having a larger range of uncorrected refractive error.

TABLE 2.3 Results from the repeated measures two-factor analysis of variance comparing the total accommodative response and mean accommodative variability (RMS) between age groups (children, adults) and by condition (blur+disparity, blur-only, disparity-only uncoupling). Additionally, a subset of children with ≤1.15 D SE (matched upper limit refractive error to adults) were also compared to the adults. The difference in least square means is presented prior to the p-value. A positive difference for the comparisons regarding the outcome variable (total accommodative response or RMS) is largest in the first group or condition listed whereas a negative difference for the comparisons indicates the first variable listed is smaller than the second group or condition listed (i.e.: Children vs. Adult, a positive difference indicates the children had a larger least squares mean than the adults). Significant p-values (< 0.05) are in bold.

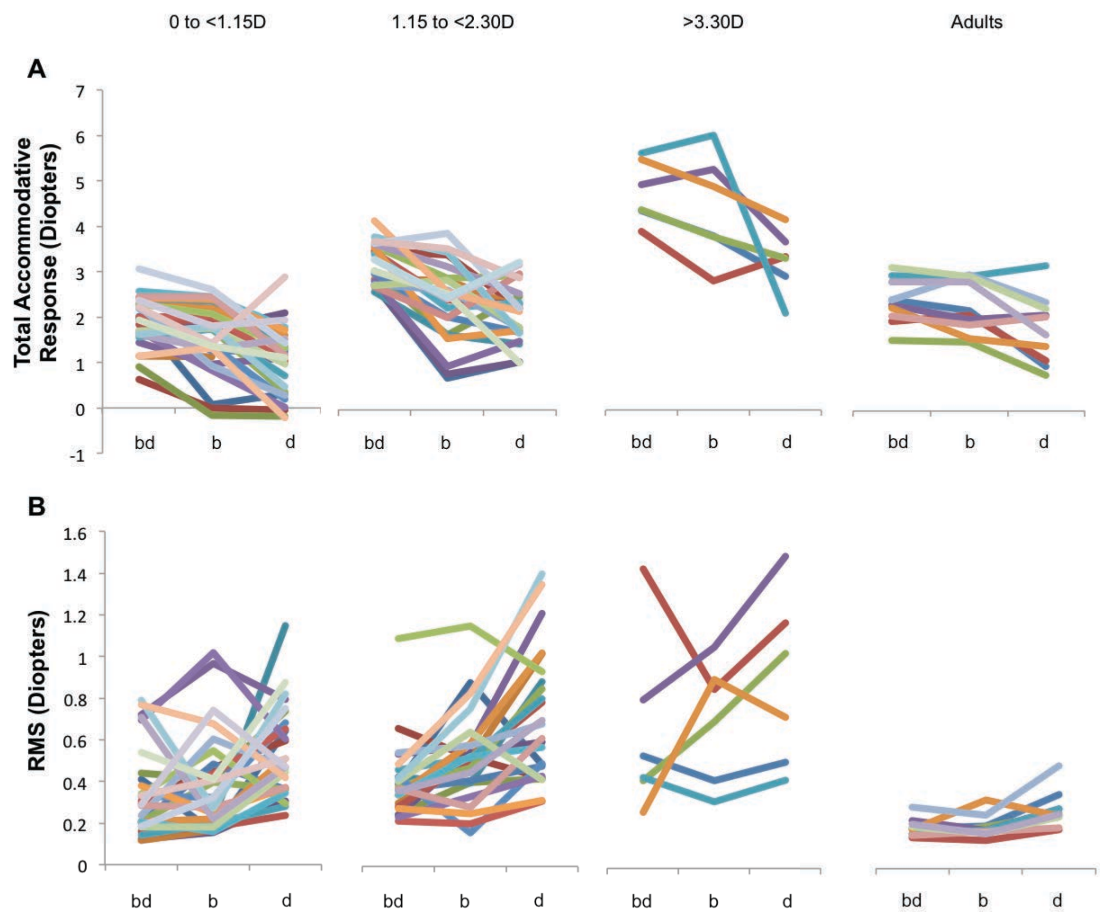
	Total Accommodative Response			RMS		
	Diff, p-value			Diff, p-value		
	All Children	Children ≤1.15D	Adults	All Children	Children ≤1.15D	Adults
Blur + Disparity Vs. Blur Only	0.59, **<0.001**	0.37, **0.001**	0.09, 0.675	-0.08, **0.019**	-0.04, 0.384	-0.01, 0944
Blur + Disparity Vs. Disparity Only	1.08, **<0.001**	0.88, **<0.001**	0.59, **0.028**	-0.24, **<0.001**	-0.18, **<0.001**	-0.09, 0.605
Blur-only Vs. Disparity-only	0.50, **<0.001**	0.51, **< 0.001**	0.50, 0.056	-0.16, **<0.001**	-0.14, **0.003**	-0.08, 0.506

		Total Accommodative Response	RMS
All Children Vs. Adults	Blur+disparity	0.41, 0.251	0.21, **0.010**
	Blur-only	-0.07, 0.847	0.28, **<0.001**
	Disparity-only	-0.07, 0.854	0.36, **<0.001**
Children ≤ 1.15 D vs. Adults	Blur+disparity	-0.49, 0.060	0.17, **0.022**
	Blur-only	-0.77, **0.004**	0.20, **0.007**
	Disparity-only	-0.77, **0.003**	0.26, **<0.001**

2.3.3 Exploration of Changes in the Accommodative Response and RMS in Individual Subjects across Cue Conditions

The relationship between the changes in the total accommodative response and changes in RMS for the three experimental conditions (blur+disparity, blur-only, and disparity-only) at 33 cm were evaluated in individual subjects. The data were not analyzed statistically but were assessed for descriptive purposes with children divided into bins based on magnitude of hyperopic refractive error (Figure 2.3). As seen in the top row of Figure 2.3, relative to the blur+disparity condition, most children had little or no decrease in total accommodative response during the blur-only condition, and the largest decrease in total accommodative response occurred in the disparity-only condition. A similar trend was noted for all levels of refractive error and for the adult subjects as well. The bottom row of the figure illustrates that despite the decrease in the accommodative response in the blur-only and disparity-only conditions, RMS increased for many subjects in both conditions, with greatest increases in the accommodative response occurring in the disparity-only condition. The adults had little to no change in RMS between the blur+disparity and blur-only condition but tended to have a decrease in RMS during the disparity-only condition. These trends are also seen at the group level in Figure 2.2.

FIGURE 2.3 Total accommodative response in the vertical meridian of the eye (A) and RMS (B) for each individual subject is plotted for each condition at 33 cm. The children are divided in columns by spherical equivalent refractive error of the right eye. The adults are shown in the last column for comparison.



While there are clear trends in the data, it is also evident that not all subjects had the same relationship between the total accommodative response and RMS across the conditions. To develop a better understanding of the various changes in the relationship between the total accommodative response and RMS relative to the blur+disparity condition, the frequency for which those relationships occurred was evaluated. The accommodative response and RMS were considered to have increased or decreased in the blur-only and disparity-only conditions relative to the full cue blur+disparity condition if there was a change of > ± 0.27 D in the accommodative response and > ± 0.08 D in RMS (values used were determined in the controls studies section A.1.3.1.1 to represent actual changes in the accommodative response and variability). The data are summarized for all children, children with similar upper limit of refractive error to the adults, and adults in Table 2.4.

TABLE 2.4 Change in total accommodative response and RMS classified using 0.27 D and 0.08 D thresholds, respectively, by age group and condition (blur+disparity, blur-only, and disparity-only) relative to the blur+disparity condition. Cell values represent subject counts and percentages in parentheses. The lighter shaded cells represent the expected relationship between RMS and total accommodative response if the changes in RMS were solely from noise in the accommodative plant. The darker shaded cells represent the total number of children who exhibited the particular characteristic in the row or column being summed.

		Blur-only				Disparity-only			
		Accomm Decrease	Accomm Increase	Accomm noChange	SUM	Accomm Decrease	Accomm Increase	Accomm noChange	SUM
All Children	RMS decrease	7 (12.01%)	1 (1.72%)	2 3.45%)	**10 (17.24%)**	4 (7.02%)	0 (0%)	1 (1.75%)	**5 8.77%)**
	RMS increase	19 (32.76%)	1 (1.72%)	5 (8.62%)	**25 (43.10%)**	37 (64.91%)	2 (3.51%)	3 (5.26%)	**42 (73.68%)**
	RMS noChange	9 (15.52%)	0 (%)	14 (24.14%)	**23 (39.66%)**	10 (17.54%)	0 (0%)	0 (0%)	**10 (17.54%)**
	SUM	**35 (60.34%)**	**2 (3.45%)**	**21 (36.21%)**		**51 (89.47%)**	**2 (3.51%)**	**4 (7.02%)**	
Children ≤1.15D	RMS decrease	3 (10.71%)	0 (0%)	2 (7.14%)	**5 (17.86%)**	2 (7.41%)	0 (%)	1 (3.70%)	**3 (11.11%)**
	RMS increase	7 (25%)	0 (0%)	3 (10.71%)	**10 (35.71%)**	16 (59.26%)	1 (3.70%)	1 (3.70%)	**18 (66.67%)**
	RMS noChange	3 (10.71%)	0 (0%)	10 (35.71%)	**13 (46.41%)**	6 (22.22%)	0 (0%)	0 (0%)	**6 (22.22%)**
	SUM	**13 (46.4%)**	**0 (0%)**	**15 (53.6%)**		**6 (60%)**	**0 (0%)**	**4 (40%)**	
Adults	RMS decrease	0 (0%)	0 (0%)	0 (0%)	**0 (0%)**	0 (0%)	0 (0%)	0 (0%)	**0 (0%)**
	RMS increase	1 (10%)	0 (0%)	0 (0%)	**1 (10%)**	2 (20%)	0 (0%)	2 (20%)	**4 (40%)**
	RMS noChange	1 (10%)	1 (10%)	7 (70%)	**9 (90%)**	4 (40%)	0 (0%)	2 (20%)	**6 (60%)**
	SUM	**2 (20%)**	**1 (10%)**	**7 (70%)**		**6 (60%)**	**0 (0%)**	**4 (40%)**	

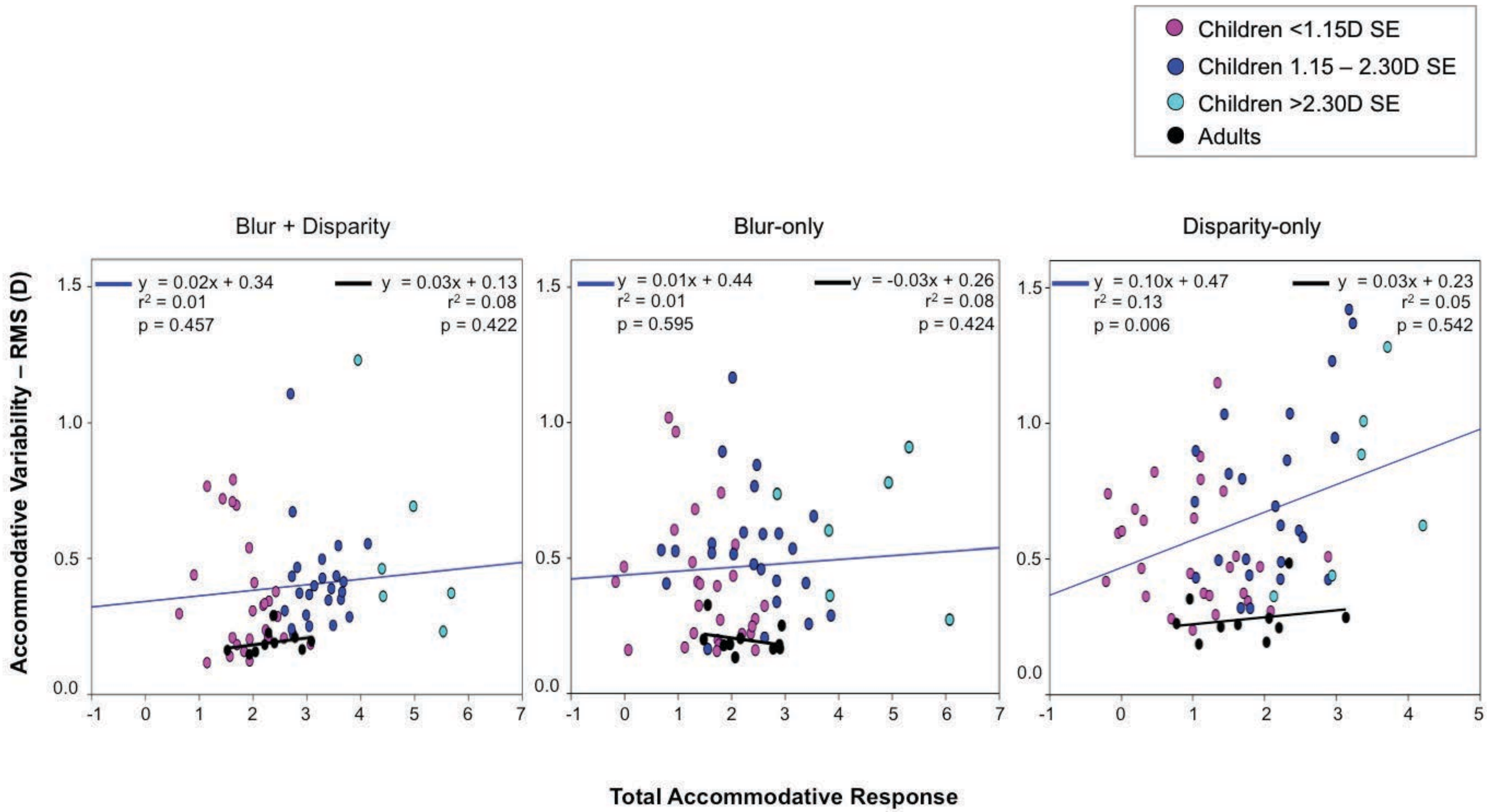
*The increase and decrease in the accommodative response and RMS for each condition are relative to the blur+disparity condition.

In the blur-only condition, 60% (35/58 total subjects) of the children had a decrease in accommodative response of more than 0.27 D whereas 90% (51/57 total subjects) of children had a decrease in the accommodative response in the disparity-only condition relative to the blur+disparity condition. Of the children who had a decrease in the accommodative response, 54% (19/35 subjects) manifested a coinciding increase in RMS in the blur-only condition and 73% (37/51) had an increase in RMS in the disparity-only condition. The adults did not appear to be as affected by removing disparity cues from the blur+disparity condition as only 20% of them had a decreased accommodative response in the blur-only condition, contrasted to the 70% who had no change in either the accommodative response or RMS in the blur-only condition compared to the blur+disparity condition. However, for the disparity-only condition 60% of the adults had a decrease in the accommodative response while the remaining 40% had no change in the accommodative response. Similar to the blur-only condition, the majority of the adult subjects did not have a change in RMS in the disparity-only condition as compared to the blur+disparity condition. The children with refractive errors not exceeding the upper limit of the adults were evaluated separately. Even when considering children with lesser amounts of hyperopia, the children's accommodative behavior still appeared to differ from that of the adults and followed the same trends seen when all children were grouped together for both the blur-only and disparity-only conditions.

2.3.4 Changes in RMS as a Function of Total Accommodative Response within Cue Conditions in Children and Adults

Regression analyses were performed to determine if there was a significant relationship between RMS and the total accommodative response within each of the three viewing conditions in both the children and adults. The results are plotted in Figure 2.4 with the children sub-divided by refractive error (≤ +1.15 D (similar upper limit SE to adults), > +1.15 to ≤ 2.30 D (twice the upper-limit SE of the adults, and > +2.30 D (remaining children)). In the children, despite the largest mean total accommodative response being measured in the blur+disparity condition, an increase in RMS was only significantly associated with an increase in the total response in the disparity-only condition for both unadjusted ($p = 0.006$) and age-adjusted linear regressions ($p = 0.009$). A significant relationship was not found between RMS and total accommodative response for either the blur+disparity condition (unadjusted $p = 0.457$, age-adjusted $p = 0.701$) or the blur-only condition (unadjusted $p = 0.595$, age-adjusted $p = 0.498$). In the adults, a significant relationship was not detected between RMS and the total accommodative response for the blur+disparity condition ($p = 0.422$), disparity-only ($p = 0.542$) or blur-only ($p = 0.424$) conditions.

FIGURE 2.4 Root mean square (RMS) plotted as a function of the total accommodative response for the blur+disparity, blur-only, and disparity-only conditions at 33 cm in the children and adults. The RMS data for the children are represented by the pink, blue and turquoise circles based on each individual's refractive error, while the adult subjects are represented by the black circles. The green regression line represents all children while the black regression line represents the adults.


Children <1.15D SE
Children 1.15 – 2.30D SE
Children >2.30D SE
Adults
Blur + Disparity
Blur-only
Disparity-only
Accommodative Variability – RMS (D)
Total Accommodative Response
y = 0.02x + 0.34
r² = 0.01
p = 0.457
y = 0.03x + 0.13
r² = 0.08
p = 0.422
y = 0.01x + 0.44
r² = 0.01
p = 0.595
y = -0.03x + 0.26
r² = 0.08
p = 0.424
y = 0.10x + 0.47
r² = 0.13
p = 0.006
y = 0.03x + 0.23
r² = 0.05
p = 0.542

2.3.5 Comparisons of Accommodative Response and RMS between Children and Adults and Under Viewing Conditions when Cues are Uncoupled

The means and standard deviations for the total accommodative response and RMS values for the blur+disparity at 33 cm, lens-induced uncoupled condition (-2.00 D lenses at 100 cm) and prism induced uncoupled condition (2 MA base-out prism at 33 cm) are presented in Table 2.2. Two-factor repeated measures ANOVA was used to investigate the changes in the total accommodative response and RMS across conditions and age group (children versus adults) (Table 2.5).

TABLE 2.5 Results from the repeated measures two-factor analysis of variance comparing the total accommodative response and mean accommodative variability (RMS) between age groups (children, adults) and by condition (blur+disparity, lens-induced uncoupling, prism-induced uncoupling). As done previously, a subset of children with ≤1.15 D SE (similar upper limit refractive error to adults) were also compared to the adults. The difference in least square means is presented prior to the p-value. A positive difference for the comparisons regarding the outcome variable (total accommodative response or RMS) is largest in the first group or condition listed in the first column, whereas a negative difference for the comparisons indicates the first variable listed is smaller than the second group or condition listed (i.e.: children vs. adult, a positive difference indicates the children had a larger least squares mean than the adults). Significant p-values (< 0.05) are in bold.

		Total Accommodative Response			RMS		
		Diff, p-value			Diff, p-value		
		All Children	Children≤1.15 D	Adults	All Children	Children≤1.15 D	Adults
Blur + Disparity Vs. Lens-induced decoupling		0.78, **<0.001**	0.61, **<0.001**	0.38, 0.164	-0.07, 0.184	-0.05, 0.389	-0.09, 0.682
Blur + Disparity Vs. Prism-induced decoupling		-0.43, **<0.001**	-0.50, **<0.001**	-0.36, 0.106	-0.09, 0.090	-0.05, 0.466	-0.09, 0.538
Lens-induced decoupling Vs. Prism-induced decoupling		-1.21, **<0.001**	-1.11, **<0.001**	-0.74, **0.003**	-0.02, 0.611	<-0.01, 0.932	<0.01, 0.996
All Children Vs. Adults	Blur+disparity	0.41, 0.301			0.19, **0.021**		
	Lens-induced decoupling	0.01, 0.971			0.17, **0.040**		
	Prism-induced decoupling	0.49, 0.220			0.19, **0.021**		
Children ≤ 1.15 D Vs. Adults	Blur+disparity	-0.44, 0.074			0.16, **0.031**		
	Lens-induced decoupling	-0.67, **0.008**			0.12, 0.098		
	Prism-induced decoupling	-0.30, 0.230			0.11, 0.124		

In the children, the mean total accommodative response was significantly higher ($p < 0.001$) in the prism-induced uncoupled cue condition as compared to the blur+disparity viewing condition and the lens-induced uncoupled cue condition. The total accommodative response was significantly larger ($p < 0.001$) in the blur+disparity condition than the lens-induced uncoupled cue condition. There were no significant differences detected ($p > 0.09$) in RMS values between the blur+disparity, prism-induced uncoupled cue condition and the lens-induced uncoupled cue condition. In the adults, the mean accommodative response was significantly higher ($p = 0.003$) in the prism-induced uncoupled cue condition than the lens-induced uncoupled cue condition. A significant difference was not detected between the prism-induced uncoupled cue condition and the blur+disparity viewing condition ($p = 0.106$) or between the blur+disparity condition and the lens-induced uncoupled cue condition ($p = 0.164$). Similar to the children, there were no significant differences detected ($p > 0.538$) in RMS values between the blur+disparity, prism-induced uncoupled cue condition and the lens-induced uncoupled cue condition.

When comparing all children to adults, a significant difference in the total accommodative response was not detected in any of the comparisons between blur+disparity, prism-induced or lens-induced uncoupled cue conditions ($p > 0.220$). However, the children had significantly higher RMS values in the blur+disparity ($p = 0.021$), lens-induced ($p = 0.040$) and prism-induced uncoupled cue ($p = 0.021$) conditions than the adults. Similar to the above comparisons, these findings also demonstrate a difference in RMS between children and adults with matched accommodative response, but not matched accommodative accuracy. Because the adults had significantly lower cycloplegic spherical equivalent refractive error than the children, a similar total accommodative response between groups suggests that the children have a less accurate accommodative response during the task than the adults. To isolate differences in accommodative response and RMS between the children and adults that are secondary to age, rather than a difference in refractive error distribution, the repeated measures ANOVA was performed again by comparing adults with only children with a matched upper limit of refractive error (≤ +1.15 D SE).

When comparing the children and adults with the upper limit of the refractive error matched between groups, a significant difference in total accommodative response was not detected in the blur+disparity condition (p = 0.074) or the prism-induced uncoupled cue condition (p = 0.226). There was however a significant difference in the lens-induced uncoupled condition between the children and the adults (p = 0.008). When comparing RMS values between the children and the adults with similar refractive error, RMS remained significantly larger in the children for the blur+disparity condition (p = 0.031), whereas a significant difference was not detected between the children and adults in either the lens-induced (p = 0.098) or prism-induced (p = 0.124) uncoupled cue conditions.

2.3.6 Associations between RMS and Pupil Size under All Viewing Conditions

Pairwise correlations were performed to determine if RMS and pupil size were significantly associated with one another, as pupil size is known to impact RMS when the pupil size is less than 3 mm (Gray, Winn et al. 1993). The mean pupil sizes for the subjects are reported in Table 2.2. No significant correlation was detected between pupil size in the children or adults for the mean RMS values for any condition (blur+disparity [children: r = -0.23, p = 0.08; adults: r = -0.45, p = 0.19], blur-only [children: r = -0.16, p = 0.23; adults: r = 0.03, p = 0.94], disparity-only [children: r= -0.13, p = 0.34; adults: r = -0.16, p = 0.66], lens-induced uncoupled cue [children: r = -0.11, p = 0.45; adults: r = -0.05, p = 0.90], or prism-induced uncoupled cue [children: r = -0.23, p = 0.08; adults: r = -0.24, p = 0.54]) and thus were not likely to impact any of the results for any of the conditions.

2.4 Discussion

The results of this study are in agreement with previous studies that have shown that RMS increases with increasing accommodative effort when comparing RMS under similar viewing conditions (e.g. blur+disparity at 100 cm to blur+disparity at 33 cm, blur-only at 100 cm to blur-only at 33 cm, disparity-only at 100 cm to blur-only at 33 cm) as shown in Figure 2.2 in both children and adults. However, the results of this study also demonstrate that in children, RMS increased when blur and disparity cues were systematically removed from the stimulus (Figure 2.2, Table 2.3). Unlike the children, the RMS values in the adult subjects were not significantly affected by removing blur and disparity cues from the stimulus (Figure 2.2, Table 2.3). While the removal of visual cues impacted RMS in the children, RMS was not impacted in children or adults when blur and disparity cues where uncoupled in the lens-induced and prism-induced uncoupled cue conditions.

2.4.1 Change in RMS with Increased Accommodative Demand

As with previous studies (Kotulak and Schor 1986, Winn, Pugh et al. 1990, Candy and Bharadwaj 2007, Anderson, Glasser et al. 2010, Yao, Lin et al. 2010), we have found that an increase in RMS has been associated with an increase in accommodative response under similar viewing conditions (Table 2.2). A possible explanation for an increase in RMS with an increase in response could be from increased noise in the accommodative plant, which would suggest an underlying mechanism in the motor (i.e.: efferent) system as previously suggested (Kotulak and Schor 1986, Gray, Winn et al. 1993). The motor theory would suggest that an increase in the accommodative response results in an increase in accommodative variability, due to the physical properties of the accommodative plant (Kotulak and Schor 1986, Gray, Winn et al. 1993). As accommodation increases, tension from the lens zonules that extend from the ciliary body to the crystalline lens lessen, allowing the lens to take on a more convex shape thus increasing the power of the lens (Remington and Remington 2012). It is thought that as the zonules are relaxed there is less tension on the crystalline lens, allowing the lens to be freer to oscillate, thus resulting in greater RMS values (Kotulak and Schor 1986). While an underlying motor mechanism is a reasonable explanation for an increase in RMS, an alternative mechanism involving the sensory (i.e.: afferent) visual system should also be considered.

It has been shown in both children and adults that as accommodative demand increases, the magnitude of the accommodative lag increases as well (Gwiazda, Thorn et al. 1993, Abbott, Schmid et al. 1998, McClelland and Saunders 2004, Anderson, Glasser et al. 2009, Roberts, Anderson et al. 2015). In addition to an accommodative lag being observed at increased accommodative demands, it has been observed that the depth-of-focus increases as well (Yao, Lin et al. 2010). It has also been shown that an increase in depth-of-focus is associated with an increase in RMS (Gray, Winn et al. 1993, Yao, Lin et al. 2010). Therefore, while it is feasible for RMS to increase secondary to a motor mechanism (i.e.: increase in noise in the accommodative plant), an increase in RMS may also arise secondary to a sensory mechanism (i.e.: increase depth-of-focus).

Considering both a motor and sensory mechanism in the context of the work in this chapter, it would be expected there would be an increase in the RMS with an increase in accommodative response if the motor mechanism was the cause of increases in RMS and that there would be an increase in RMS with an increase in accommodative lag if the sensory mechanism was the cause of increases in RMS. When examining the relationship between RMS and total accommodative response it is apparent that the magnitude of RMS increased along with an increase in the total accommodative response from the 100 cm to 33 cm viewing distances for all conditions, which would be supportive of an underlying motor mechanism. However, while the total accommodative response increased between the 100 cm and 33 cm viewing distances for all conditions so did the lag of accommodation, suggesting a sensory mechanism may also be contributing to the increase in RMS. Additionally, when viewing the stimuli where accommodation and vergence were coupled (blur+disparity, blur-only, and disparity only), at the group level (Figure 2.2, Table 2.2), as well as the individual level (Figure 2.3 and Table 2.4), the children had the greatest accommodative response when viewing the stimulus binocularly (blur+disparity condition) with both blur and disparity cues available, yet RMS values were smallest in the blur+disparity condition. Also, the children generated the smallest accommodative response (i.e.: largest lag) in the disparity-only condition where the subjects viewed a low spatial frequency DOG target devoid of spatial cues to stimulate accommodation. This suggests that in addition to RMS increasing with an increase in accommodative response when cues are matched (blur+disparity at 100 compared to blur+disparity at 33), RMS is also influenced by other sensory and neural factors.

DOG stimuli have been shown to open the accommodative loop (Kotulak and Schor 1987, Tondel and Candy 2008), which increases the depth-of-focus of the eye (Kotulak and Schor 1987), thus giving accommodation a wider range in which to fluctuate. It has been shown that in adults, accommodative variability (i.e.: accommodative microfluctuations) is less than the depth-of-focus of the eye and may act as sub-threshold blur detectors (Kotulak and Schor 1986, Yao, Lin et al. 2010). Thus, if the depth-of-focus of the eye increases, accommodation is able to fluctuate more without the accommodative control system detecting blur, resulting in a larger RMS. In the disparity-only condition, the children with greater amounts of hyperopia had the largest RMS values, likely because they have a greater range over which to relax their accommodation due to their far point being further than others with lesser amounts of uncorrected hyperopia.

Unlike the children, a significant difference in RMS was not detected in adults between the blur+disparity, blur-only and disparity conditions, despite a significantly smaller accommodative response in the disparity-only condition as compared to the blur+disparity condition. In adults, it has been shown that when a stimulus is viewed monocularly and the accommodative loop is opened, accommodation goes to its dark focus, which is approximately ~1-2 D (Baker, Brown et al. 1983, Tucker and Charman 1986, Rosenfield, Chiu et al. 1994). Given that the DOG stimulus has been shown to open the accommodative loop (Kotulak and Schor 1987, Tondel and Candy 2008), accommodation retreating to its resting position during the disparity-only condition could account for the lack of a difference found in adults between the blur-only and disparity-only conditions as a 1-2 D response in the disparity-only condition would be similar to the accommodative responses in the other conditions. However, it is evident in Figure 2.2 that the adults exhibited an increase in their accommodative response when the DOG stimulus was viewed at 33 cm as compared to 100 cm, suggesting that accommodation was not at its resting condition when viewing the DOG stimulus. Thus, given that the stimulus was viewed binocularly in this study, the difference in accommodative behavior between the children and adults in the disparity-only viewing condition may be that adults are better at processing the remaining visual cues (i.e.: proximal, disparity) than children in order to stabilize the accommodative response when other cues (such as blur) are removed from the stimulus.

The results also suggest that the manner in which the total accommodative response is defined and subsequently analyzed will impact the interpretation of the relationship between the total accommodative response and RMS. It was hypothesized that children with increased levels of hyperopia would have increased RMS if they accommodated through their hyperopia. Figure 2.4 illustrates that the children with greatest amounts of hyperopia also had the greatest measures of total accommodative response. However, regression analysis did not detect a significant relationship between RMS and total accommodative response when the total accommodative response was analyzed across subjects. Yet, as discussed above, when the total accommodative response was investigated within-subjects and the total accommodative response was calculated as a change in distance to near for each subject, a significant difference was detected. Interestingly, the only inter-subject regression analysis that did detect a significant relationship between RMS and an increase in total accommodative response was in the disparity-only condition, likely due to the lack of blur cues and greater depth-of-focus, as discussed above.

2.4.2 Impact of Disparity on the Total Accommodative Response and RMS When Blur Cues are Present

In the children, the mean accommodative response was less when the subjects viewed the stimulus monocularly in the blur-only condition as compared to viewing the stimulus binocularly in the blur+disparity condition, suggesting that disparity may play a significant role in accommodative accuracy when blur-cues remain present in the stimulus as suggested by others (Turner, Horwood et al. 2002, Bharadwaj and Candy 2008, Horwood and Riddell 2009, Horwood and Riddell 2013). The decrease in the total accommodative response between the blur+disparity and blur-only condition was apparent using all children in the analysis, as well as when only children with ≤1.15 D of spherical equivalent refractive error were analyzed. The adults on the other hand, did not have a statistically detectable difference in the accommodative response between the blur+disparity and blur-only conditions. There are different explanations that may account for the difference in the accommodative response between the children and the adults in the absence of disparity. One explanation for the larger accommodative lag in children as compared to the adults may be that children are more reliant on multiple visual cues to process visual information to generate their most accurate accommodative response and thus the removal of a cue, such as disparity, results in a decrease in the accommodative response. Another potential explanation for the difference in accommodative lag between the children and adults in the blur-only condition is that children (age 2 to 7 years) have been shown to have larger CA/C ratios than adults (Babinsky, Sreenivasan et al. 2015), and thus is it may be more detrimental to the accommodative response in children as compared to adults when cues to vergence (i.e.: disparity) are removed from the stimulus. It should be noted however, that while there was a significant difference in CA/C ratios found between the children and the adults in the study cited above, more than half of the children tested had CA/C (convergence accommodation/convergence) ratios in the same range as the adults tested and thus the impact from CA/C may not apply to all children. The children in this study also had larger RMS values when the stimulus was viewed monocularly and the disparity-cues were absent, suggesting that children may be more dependent on vergence not only for more accurate accommodative responses (Turner, Horwood et al. 2002, Bharadwaj and Candy 2008, Horwood and Riddell 2009, Horwood and Riddell 2013), but also for more stable accommodative responses (Campbell, Robson et al. 1959, Toates 1972), particularly if the proposed sensory mechanism influences the stability of the accommodative response.

2.4.3 Impact of Uncoupled Blur and Disparity Cues on RMS

To further investigate the impact of visual cues on the variability of the total accommodative response, subjects viewed the stimulus while blur and disparity cues were uncoupled using minus lenses at 100 cm and base-out prism at 33 cm. While there was a difference in the total accommodative response across conditions with the largest mean total accommodative response being in the prism-induced uncoupled condition and the least mean total accommodation response being in the lens-induced uncoupled condition, a significant difference in RMS was not detected in the children or adults for any of the comparisons across conditions (Table 2.5). These results suggest that RMS is unaffected when blur and disparity cues are available, despite the cues being uncoupled. Perhaps the presence of all cues, whether uncoupled or not, is adequate for both children and adults to generate stable accommodative responses. It may be more likely however, that across the three conditions, both the motor and sensory systems are contributing to the stability of the response. For example, in comparing the prism-induced condition to the blur+disparity condition, the prism-induced condition had a greater total accommodative response. The motor mechanism would suggest there would be an increase in RMS, but a more accurate response may influence the sensory system resulting in a decrease in RMS, thus balancing out the effect. There was no difference detected between the lens-induced condition and the other two conditions despite the lens induced uncoupled condition having the largest lag of all conditions measured. It has, however, been hypothesized that if the defocus is great enough, then changes in blur cannot be detected by the accommodative control system and RMS decreases (Yao, Lin et al. 2010).

2.4.4 Comparison of RMS between Children and Adults

As a group, the children in this study generated similar total accommodative responses as the adults in all conditions. However, it is apparent in Figure 2.2 that while the accommodative responses are similar, the children had less accurate accommodative responses than the adults due to their larger amounts of uncorrected hyperopia. When comparing only children with similar upper limit refractive error to the adults (≤ 1.15 D SE), the children had significantly lower total accommodative responses than adults in the blur-only, disparity-only, and lens-induced uncoupled condition. The children also had significantly larger RMS values than the adults in the blur+disparity, blur-only and disparity-only conditions, when comparing all children to adults and when only comparing children with similar refractive errors. The adults in this study appeared to be able to adapt their accommodative behavior throughout the various viewing conditions (removal of cues and decoupling of cues) to the available cues. It may be that children are able to integrate across cues but are unable to adapt as efficiently as adults when cues are removed from the stimulus. Possible sources for the differences in the total accommodative responses and RMS in the children may arise also from the children's depth-of-field (DOF) and children's ability to detect blur, points that will be explored in chapter 3. Considering RMS in the context of being sub-threshold blur detectors (Kotulak and Schor 1986), if children have a larger DOF than adults, then accommodation would be freer to vary, as demonstrated by previous studies showing increased RMS with increased DOF (Gray, Winn et al. 1993). Likewise, if children have a decreased ability to detect blur, accommodation would again be freer to vary, or vice versa. Behavioral testing has shown that even by 8 years of age, children do not have adult-like spatial vision (Bradley and Freeman 1982), and thus it is feasible they also do not have adult-like DOF or blur detection thresholds.

2.4.5 Impact of Pupil Size on RMS

It has been shown that a decrease in pupil size results in an increase in depth-of-focus in the eye (Atchison, Fisher et al. 2005) that coincides with an increase in accommodative microfluctuations when the pupil size is less than 4 mm (Gray, Winn et al. 1993). In our study, data points were excluded if the pupil size was less than 4 mm and therefore is unlikely to have affected our results. Additionally, the average pupil size of subjects for this study was > 6 mm in the children and near 5 mm and greater for the adults for all testing conditions. If having a smaller pupil had affected the study it would have been in the differences between the children and adults, as the adults had smaller pupils. However, the adults in the study had smaller RMS values than children, again suggesting that pupil size did not impact the results of our study.

2.4.6 Study Limitations

Our study is not without limitations. The first limitation of the study is that cycloplegic SE was measured on the Grand Seiko auto-refractor whereas all of the experimental measures were captured using the PR. Most children had dilated pupil sizes > 8 mm, which is outside of the operating range of the PR and thus cycloplegic measures were taken using the Grand Seiko. Additionally, 4 subjects had levels of uncorrected hyperopia that were outside of the operating range of the PR if measured under cycloplegia. While two separate instruments were used for data collection, a recent study has shown that the Grand Seiko is comparable to subjective refraction (Aldaba, Gomez-Lopez et al. 2015) suggesting that we used an appropriate value for SE. Aldaba et al (2015) also found that the PR and Grand Seiko are comparable when static accommodative measures are obtained at 40 cm, which was very similar to our working distance of 33 cm. Although, it should be stated that our measures were taken dynamically with the PR (25 Hz) while the measures in Aldaba et al (2015) were measured using sphero-cylinder static measures at a similar working distance.

An additional limitation of the study is that the PR measures accommodation in the vertical meridian only while in dynamic mode. Thus, while the total accommodative response and accommodative lag were discussed in the context of the mechanism that contributes to an increase in accommodative response, it is important to consider that these measures were discussed in the context of the vertical meridian of the right eye only. To determine the possible impact of using the vertical meridian in calculating the total accommodative response, the difference between the power of the right eye in the vertical meridian and the least plus meridian of the right eye were calculated. The median difference between the two meridians was -0.03 (interquartile range -0.16, -0.005 D) suggesting that using the vertical meridian was unlikely to bias the results. It is also unlikely that uncorrected anisometropia would have had a large impact on these findings across subjects as the mean SE anisometropia for the children was 0.29 ± 0.22 D SE (range 0.002 to 1.00 D SE) with only 8 children having > 0.50 D SE difference between the two eyes and the mean SE anisometropia in the adults was 0.31 ± 0.23 D (range of 0.06 to 0.75 D SE) with 2 adults having > 0.50 D SE. However, it is feasible that the small amount of uncorrected anisometropia and uncorrected astigmatism may add to the variability in the results, particularly in regards to the total accommodative response and magnitudes of accommodative lag as another meridian may be in better focus for some individuals.

2.4.7 Summary and Conclusions

In summary, the results of this study have confirmed other studies that have shown that when the stimulus features remain constant (no changes in cues) and the accommodative response increases, RMS increases as well. We also observed however, that while the response increased, the accommodative lag also increased, suggesting that there may be an underlying sensory mechanism that contributes to the increase in RMS in addition to the previously proposed motor mechanism (i.e.: increase noise in the accommodative plant). Subjects in this study with larger amounts of hyperopia who generated the largest total accommodative responses did not experience an increase in RMS as would be expected if increased RMS was due only to mechanical properties of the plant, which further supports the involvement of an underlying sensory mechanism (i.e.: increased lag, increased DOF). The results of this study also demonstrated that in children, the magnitude of the total accommodative response decreased while RMS increased when both blur and disparity cues were systematically removed from the visual stimulus. Interestingly, a difference was not detected in RMS when blur and disparity cues were uncoupled, despite significant differences in the magnitudes of the total accommodative response across the uncoupling conditions and the blur+disparity condition. Our results are in agreement with others that have shown that accommodative variability is larger in children than in adults not only in the presence of blur+disparity cues, but also when the cues are removed from the stimulus, suggesting children, on average, do not have a mature sensory visual processing system by 10 years of age.

CHAPTER 3: Association between Accommodative Microfluctuations, Blur Detection Thresholds and Depth of Focus in Children with Uncorrected Hyperopia

3.1 Introduction

Blur is one of the primary visual cues processed by the afferent (sensory) pathway of the visual system (Watson and Ahumada 2011), which signals the efferent (motor) pathway to produce a change in accommodation to bring the target of regard into focus (Gamlin, Zhang et al. 1994). Once the target of regard is in focus, accommodation is generally considered to be in a steady-state, however the accommodative response is not stable but rather dynamic as it oscillates around the mean response at a frequency of less than ~3 Hz (Campbell, Westheimer et al. 1958). The oscillations are referred to as accommodative microfluctuations (Charman and Heron 1988).

Microfluctuations have been studied in the context of the depth-of-focus and depth-of-field (DOF) in adults (Kotulak and Schor 1986, Gray, Winn et al. 1993, Yao, Lin et al. 2010). The depth-of-focus (retinal space) and DOF (object space) refer to the range over which object vergence can change without being detected as blur on the retina and thus initiating a change in the mean accommodative response (Wang and Ciuffreda 2006), or changing observed object clarity (Campbell 1957, Kotulak and Schor 1986, Jiang 1997). Both microfluctuations and DOF are affected similarly (increase in microfluctuations coincide with an increase in DOF) by factors such as luminance (Schor, Johnson et al. 1984, Charman and Heron 1988), pupil size (Gray, Winn et al. 1993, Atchison, Fisher et al. 2005), and spatial frequency (Niwa and Tokoro 1998). It has also been shown that as DOF and RMS increase or decrease, the accommodative response is also more or less accurate respectively (Gray, Winn et al. 1993, Yao, Lin et al. 2010). We observed similar findings in Chapter 2 as both children and adults had an increase in RMS accompanied by a greater accommodative lag at the 33 cm viewing distance as compared to the 100 cm viewing distance (Figure 2.2).

Accommodative microfluctuations have been studied in the context of the accommodative control system and have been shown to increase or decrease with corresponding changes of object vergence when the target is located within the DOF, suggesting that microfluctuations may minimize the perception of blur by acting as sub-threshold blur detectors in the accommodative control system (Kotulak and Schor 1986, Yao, Lin et al. 2010). However, if the change in object vergence reaches the edge of the depth-of-focus without a correction by the accommodative control system, the individual detects blur. Blur detection thresholds may be determined by identifying the smallest amount of change in object vergence needed to detect blur (Yao, Lin et al. 2010), or by applying blur to a stimulus (Jacobs, Smith et al. 1989, Watson and Ahumada 2011).

While microfluctuations and blur detection thresholds have been studied extensively in adults (Charman and Heron 1988, Watson and Ahumada 2011), only a few studies have investigated these in children (Schmid, Robert Iskander et al. 2002, Candy and Bharadwaj 2007, Schultz, Sinnott et al. 2009, Anderson, Glasser et al. 2010). Anderson et al. (2010) and others (Candy and Bharadwaj 2007, Schultz, Sinnott et al. 2009) have reported that the magnitude of microfluctuations decrease with increasing age from infancy to adulthood (Candy and Bharadwaj 2007, Anderson, Glasser et al. 2010) and with increasing accommodative response magnitude (Candy and Bharadwaj 2007, Anderson, Glasser et al. 2010, Yao, Lin et al. 2010). Blur detection thresholds have been investigated in myopic children as young as 8 years of age showing that myopic children have similar blur thresholds to emmetropic children (Schmid, Robert Iskander et al.

2002). To the authors' knowledge, there has yet to be an investigation of microfluctuations and blur thresholds in the same children.

Neither microfluctuations nor blur detection thresholds have been investigated specifically in children with varying amounts of uncorrected hyperopia. These children are of interest because as accommodative demand increases with the amount of uncorrected hyperopia, larger microfluctuations may occur in relation to the increased accommodative effort due to noise in the accommodative plant (Kotulak and Schor 1986) or in relation to an increase in the depth-of-focus and coinciding increase in accommodative lag that has been observed with an increase in accommodative effort (Yao, Lin et al. 2010) . In Chapter 2, we also observed an increase in microfluctuations with an increase in the accommodative response as well as an increase in accommodative lag, suggesting both motor and sensory systems influence the magnitude of accommodative microfluctuations. If microfluctuations are operating as sub-threshold blur detectors and the magnitude of the fluctuations is larger in individuals with higher amounts of uncorrected hyperopia, one would then expect that children with higher amounts of uncorrected hyperopia would have larger DOF and poorer blur detection thresholds.

Thus, the purpose of this study was to determine if blur detection threshold levels are associated with accommodative microfluctuations, age, uncorrected hyperopia or accommodative lag in children between 3 and < 10 years of age. The results in Chapter 2 revealed that while in both children and adults there was an increase in microfluctuations with an increase in accommodative response when changing the stimulus from 100 cm (1 D demand) to 33 cm (3 D demand), there was not an increase in RMS with an increase in response when comparing the blur+disparity condition to the blur-only condition (Table 2.3), as would be expected if RMS were solely the result of accommodative plant noise. Additionally, the largest RMS values measured in Chapter 2 were during the disparity-only condition where the subjects viewed a Difference of Gaussian stimulus that is devoid of blur cues (Kotulak and Schor 1987). The results from Chapter 2 suggest that RMS or the stability of the accommodative response may be influenced by other factors in addition to accommodative plant noise, such as accommodative lag. Thus, a secondary purpose of the study was to determine if accommodative microfluctuations are associated with age, uncorrected hyperopia and accommodative lag. Lastly, because blur detection thresholds and DOF values have yet to be established in young children, data were also collected on adult control subjects to serve as comparison to a mature visual system.

3.2 Methods

3.2.1 Study Subjects

Subjects aged 3 to < 10 years and non-presbyopic adult subjects were recruited from the University of Houston College of Optometry staff, student, and patient populations, as well as the local community. The study followed the tenets of the Declaration of Helsinki and was approved by the University's institutional review board for the protection of human subjects. All subjects over the age of 18 years provided written informed consent and subjects younger than 18 years provided assent while their parents provided written parental permission to participate in the study.

Prior to participation in the study, subjects or their parents (in the case of child participants) were queried to ensure subjects met the inclusion criteria of ≥ 32 weeks gestation and a birth weight ≥ 2500 grams. Subjects were also screened for the presence of exclusion criteria: history of ocular or systemic diagnoses that may impact accommodation, were taking medications known to impact accommodation, or had a history of developmental delays or behavioral diagnoses, such as attention deficit disorders. Subjects were also ineligible from participation if they had a current or previous refractive error correction or had known cycloplegic refractive error ≤ -0.50 diopters (D) spherical equivalent (SE), anisometropia > 1.00 D SE or astigmatism > 1.25 D cylinder.

In addition to participating in the experiment, all subjects had a complete vision examination performed by the investigator. The vision examination included monocular visual acuity with isolated letters with crowding bars (top, bottom, left and right positioned at one letter width from the letter) following the electronic psychometric visual acuity testing protocol established by the Pediatric Eye Disease Investigator Group (electronic HOTV (Holmes, Beck et al. 2001, Moke, Turpin et al. 2001) for subjects < 8 years and ETDRS (Beck, Moke et al. 2003) for subjects ≥8 years) presented on the M&S SmartSystem (M&S Technologies, Inc. Niles, IL) calibrated for testing at 14.5 feet. In addition to visual acuity testing, unilateral cover test was performed to rule-out strabismus. Subjects were excluded from data analysis if they did not have typical visual acuity for their age (< 20/50 for 3 to < 4 years, < 20/40 for 4 to < 5 years, < 20/32 for 5 to < 6 years (Pan, Tarczy-Hornoch et al. 2009), 20/25 or worse for subjects 6 years and older (Scheiman, Hertle et al. 2008)) or were diagnosed with strabismus (any movement seen on unilateral cover test) or amblyopia (visual acuity > 2 lines intraocular difference) (Pediatric Eye Disease Investigator 2002).

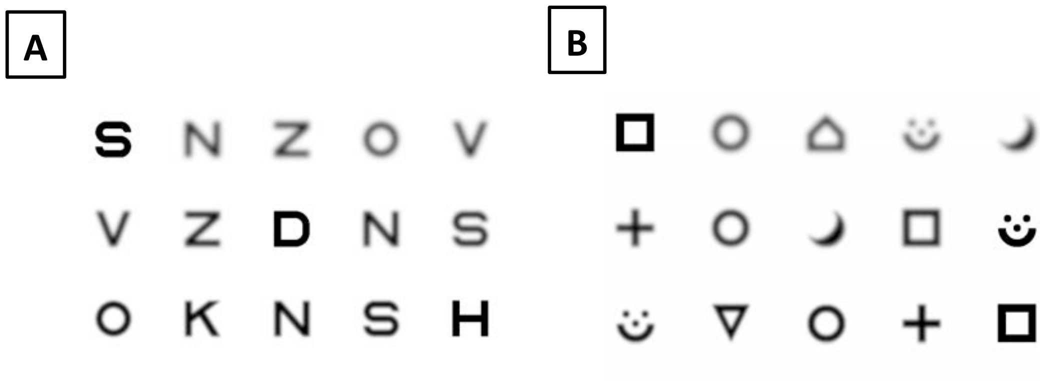
Subjects also had a cycloplegic assessment of refractive error using the Grand Seiko WAM-5500® open-field auto-refractor (RyuSyo Industrial Co., Ltd. Hiroshima, Japan), and a dilated fundus examination to rule out ocular pathology. Three measures of cycloplegic refractive error were obtained for each eye (30 minutes after instillation of 1% cyclopentolate). Each of the three measures were transformed into power vector notation, which represents the original sphero-cylinder refractive error as three powered lenses: a spherical lens power M (i.e.: spherical equivalent), and two Jackson Cross Cylinder lenses, one with power J_0 at axis 0° and the other with power J_{45} at axis 45° (Thibos, Wheeler et al. 1997). Once each of the cycloplegic measures were transformed into power vector notation, the three respective values for each vector were averaged, then the three average vectors were back-transformed to represent the mean sphero-cylinder cycloplegic refractive error for the right and left eye of each subject. The mean SE value (i.e.: mean M vector) was used to classify the refractive error of each eye as the most plus and least plus eye of each subject.

For children who were recruited from the optometry clinic, eligibility was known prior to the consent process, as the clinicians who referred the patient to the study were aware of the study inclusion/exclusion criteria. However, children recruited outside of the optometry clinic were queried and screened for the exclusion criteria regarding previous diagnoses and medications prior to the laboratory visit while the refractive error exclusion criteria and other vision examination criteria (described below) was determined at the vision examination, which occurred after the laboratory visit. Children identified during the vision examination to be ineligible were not included in the analysis.

3.2.2 Blur Detection Experiment

Blur detection thresholds were investigated using a five-alternative forced choice method. Custom designed blur charts were created with either shapes or Sloan letters (Pelli 1988) using Matlab (2014b) which generated a shape and letter size of 1° on an iPad Air® (Apple Inc., Cupertino, CA, 2048 x 1536 pixels) at 33 cm. Each row of the chart had one optotype with no added blur (100% contrast) while the other four optotypes were blurred by one of nine levels produced by convolution using a Gaussian kernel with standard deviations (*SD*) ranging from 0.71 to 11.31 arc minutes in $\sqrt{2}$ steps. A sample of three test lines is seen in Figure 3.1. The rows of the blur charts were displayed on the iPad Air® using Keynote® (Apple Inc., Cupertino, CA) presentation software with a viewing area of 8.9 cm (15.09º) horizontally and 4.6 cm (7.94º) vertically. The investigator controlled the presentation of the stimuli using an iPhone® (Apple Inc. Cupertino, CA). The iPad Air® was placed above a beam-splitter, which allowed the stimulus to be viewed with an optical target vergence of 33 cm while refractive error and pupil size were measured in primary gaze throughout the experiment using eccentric photorefraction. Through the beam-splitter, the blurred letter and shape optotypes had Weber contrasts of ≥ 60% with a background luminance of 5.9 cd/m^2 (Contrast: Level 9 = 60%, 8 = 69%, 7 = 98%, 6 = 99%, 5 to 1 = 99.7%), while the clear letter and shape optotypes had 99.7% contrast. The stimulus apparatus as well as the photorefractor were covered using a curtain enclosure throughout the experimental testing condition and the room lights were dimmed to limit any distractions and aid in photorefraction measurement capture. The subjects were positioned in a headrest throughout the experiments to limit head movements.

FIGURE 3.1 Three representative lines from the blur chart produced by convolution using a Gaussian kernel with standard deviations of 2.83 (bottom line), 4.00 (middle line) and 5.66 arc minutes (top line). (a) Sloan letter optotypes. (b) shape optotypes.



Prior to testing, subjects aged 6 to < 10 years were administered The San Diego Quick Assessment (La Pray M. 1969) test as a screening assessment to estimate each child's individual reading level. Children who were unable to correctly read aloud 9/10 words from the lowest level of the assessment (pre-primer) were shown the shapes, otherwise the children aged 6 to < 10 years were shown the Sloan letters. All children < 6 years were shown the shapes, irrespective of their reading ability.

Subjects were positioned in a headrest to view the optotypes through the beam splitter, and the lights were dimmed. Subjects viewed the optotypes binocularly and were instructed to tell the investigator which shape or letter in the row was the clearest. For the youngest children the question "which one is not fuzzy?" was also asked if the subject did not understand the word "clear." Additionally, all children who viewed the shapes went through a training session prior to testing to ensure they understood the task of choosing the clearest shape. For the older children and adults, there was no training session prior to the task.

The shapes were presented one row at a time with a maximum of four presentations of each blur level to minimize distraction and maximize subject attention and participation. The lowest three blur levels (0.71', 1.00', and 1.41' Gaussian standard deviations) were presented three times each to minimize frustration for the youngest children (3 to < 6 years) as they approached the threshold for the shape stimuli. For the letter stimuli used with the older participants, three rows of blur levels were displayed at one time and each blur level was presented to the subject a total of 5 times. For both sets of stimuli, the subjects viewed the blur lines in order from easiest to most difficult. Once the child completed the most difficult level of one chart, a new chart was displayed either one row at a time for the shapes or 3 rows at a time for the letters going from most to least blurred. No time limit was placed on the subjects during testing. The blur detection thresholds were determined by fitting the observed data to a psychometric function using Probit analysis (Finney 1947) with the threshold defined as 60% correct.

3.2.3 Depth-of-Field Experiment

Subjects who participated in the blur detection experiment and were ≥ 6 years of age also participated in the DOF experiment. Subjects monocularly viewed either two capital letter X's placed horizontally or three capital letter Y's placed vertically and etched onto a clear piece of glass with a laser. Each letter subtended 0.21º with 0.2 mm stroke width at 33 cm. The letters were spaced 0.21º apart from one another so that if the two glass plates were on top of each other, the X's and Y's formed a cross subtending 1.4º x 1.4º. The letters were displayed using an optical bench at 33 cm directly in front of the right eye while the left eye was occluded using a Kodak 89B Wratten gelatin filter that blocks visible light. A blank, white slide (5.9 cd/m^2) was displayed on the iPad Air® at 90 cm in front of the subject through a beam-splitter to provide high contrast between the black fixation letters and the screen. The PowerRef II (PR) (Plusoptix Inc., Atlanta, GA) recorded refractive error, eye alignment and pupil size throughout the experiment. The room lights were dimmed to limit any distractions and aid in photorefraction measurement capture. The subjects were positioned in a headrest throughout the experiments to limit head movements. (Note: A curtain was not used to cover the side of the experimental set up in the DOF experiment as was done for all previous experiments as the investigator needed to be able to manipulate the stimuli throughout the experiment as described below.)

Both the proximal and distal edges of the DOF were measured with a natural pupil and normal accommodation with the order (distal vs. proximal) being counter-balanced across subjects. For the distal limiting position of the DOF, the subject viewed the vertical “Y’s” while the investigator placed the row of the three horizontal X’s far enough from the subject that, while maintaining focus on the “Y’s”, the subject reported the X’s were blurred. The subjects were instructed to keep the “Y’s” clear at all times but to *notice* when the “X’s” became “clear just like the “Y’s.” The investigator then moved the “X’s” toward the “Y’s” at a rate of ~0.5 cm/second. The distance at which the subject reported the “X’s” were clear like the “Y’s” was recorded as the distal edge of the DOF. The procedure was repeated 5 times. A similar testing procedure was employed for the proximal limiting condition, except that subjects viewed the “X’s” at 33 cm and were instructed to keep them clear at all times while the “Y’s” were initially placed near the subject then moved away from the subject towards the “X’s”. The distance at which the subject reported the “Y’s” were clear like the “X’s” was recorded as the proximal edge of the DOF. Each subject performed practice trials to confirm the subject was able to understand and complete the task.

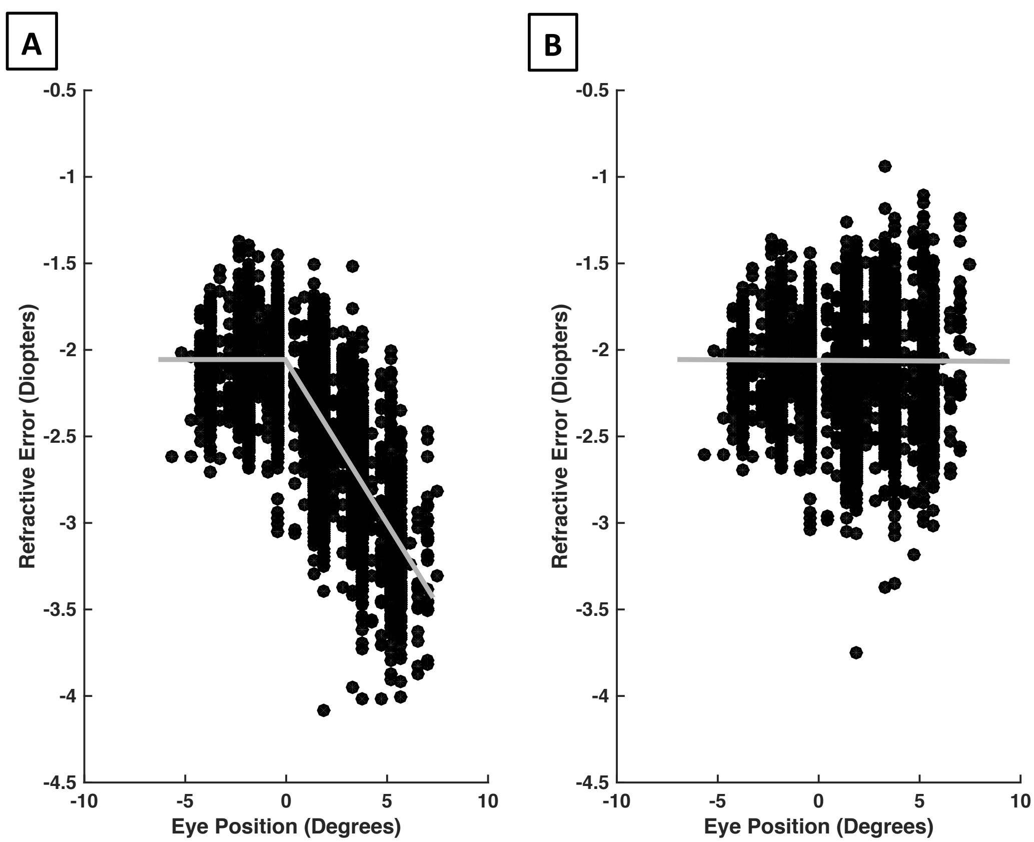
3.2.4 Measures of Refractive Error and Pupil Size

Changes in refractive error, eye alignment and pupil size were measured in both eyes during the blur detection experiment and the right eye only in the DOF experiment using the PR. The method of eccentric photorefraction has been described in detail elsewhere (Schaeffel, Wilhelm et al. 1993, Gekeler, Schaeffel et al. 1997, Choi, Weiss et al. 2000) and in Appendix A. Prior to experimental testing, each individual underwent a trial lens calibration for each eye to obtain more precise measures of refractive error, described in detail in Appendix A.

Photorefraction data were filtered offline to eliminate outlying data points that are known to be outside of the working range of the PR or points that are unlikely to be physiological in nature (i.e.: large fluctuations secondary to a blink). Measures of refractive error were removed if the change in focus between two data points were > 10 D/second (Harb, Thorn et al. 2006), refractive error measures were < -6.00 D or > +4.00 D (Gekeler, Schaeffel et al. 1997, Choi, Weiss et al. 2000), pupil size was < 4 mm or > 8 mm, and gaze position outside of ± 10° horizontally or ± 5° vertically to eliminate erroneous measures from peripheral refraction (Jennings and Charman 1981, Navarro, Artal et al. 1993) and as recommended by the manufacturer for the first generation PowerRefractor (Multi Channels Systems, Reutlingen Germany).

Our laboratory had previously examined the effect of horizontal eye position on refractive error values measured by the PR during a reading task and found a significant association between horizontal eye position and refractive error measures. A similar relationship was found in the present study in both children and adults, as the experiment required scanning horizontal eye movements across the width of the viewing area. A sample plot showing the relationship between horizontal eye position and refractive error measures obtained by the PR from an adult subject is shown in Figure 3.2a. The data had a bi-linear distribution with the junction of the two slopes at approximately zero degrees for both the right and left eyes for all subjects. To determine the appropriate correction factor for each subject, piecewise linear regression was performed on each eye of each individual subject to determine the slope of the refractive error and eye position functions (slope $\leq 0°$ and slope $> 0°$). Each eye position datum point was then multiplied by the slope of the respective regression line ($\leq 0°$ or $> 0°$) and the product was subtracted from the corresponding refractive error datum point. The effect of the correction factor for the same subject in Figure 2a is shown in Figure 3.2b.

FIGURE 3.2 Representation of the relationship between refractive error and eye position of a typical adult subject before and after the eye position correction factor was applied to the refractive error data. A) Refractive error plotted as a function of horizontal eye position prior to applying the correction factor to the data. The gray lines represent the change in slope of the data when eye position is ≤ 0° and > 0°. B) Refractive error as a function of eye position after the eye position correction has been applied, illustrating the effectiveness of the correction factor.



3.2.5 Data Analysis

The variability of the accommodative response was calculated using the root mean square (RMS) (Gray, Winn et al. 1993) of the measured refractive error from the PR throughout the experiment. The refractive error data were binned every 10 seconds to minimize the chance of analyzing drifts in accommodation given the experiment took > 1 minute to complete (children 3.0±1.0, adults 1.6±0.4 minutes). Next, RMS was calculated for each bin and the mean RMS was calculated across bins. The mean RMS value for each subject is used in all analyses in this chapter and is referred to throughout the chapter as RMS. The accommodative lag was calculated as the mean difference between the average calibrated refractive error in the vertical meridian of the eye during the experiment and the accommodative demand of 3 D. The DOF for each subject was calculated as the difference in dioptric space between the average measures (5 trials) of the distal and proximal edges of the DOF.

Comparisons between children and adults for SE, blur detection thresholds, RMS and DOF were performed using two-sample unpaired t-tests. Spearman correlation was used to assess the relationship between the outcome variable blur detection threshold and the independent variables RMS, SE, age, and accommodative lag. Multivariable linear regression was then used to assess the relationship between blur detection thresholds and RMS while controlling for potential confounders age, SE, and accommodative lag. Given that RMS is thought to be a sub-threshold blur detector, Spearman correlations and multivariable linear regressions were repeated to assess the relationships between RMS and age, SE and accommodative lag. The classification of ametropia was based on the most plus eye and thus measures from the most plus eye (as obtained from cycloplegic auto-refraction) were used for all comparisons concerning accommodative measures from the blur detection task as done in previous studies of children with uncorrected hyperopia (Rosner and Rosner 1987, Wen, Tarczy-Hornoch et al. 2013). The DOF experiment was conducted on the right eye of all subjects and thus analyses involving the DOF experiment (DOF and pupil size) are from the right eye. Data analysis was performed using Stata® version 12.1 (StataCorp 2015).

3.3 Results

Seventy-six subjects (66 children and 10 adults) were recruited to participate in the study. Of the sixty-six children recruited, seventeen were excluded from data analysis (3 did not have cycloplegic refractive error measures; 1 did not have a valid calibration for her most plus SE eye; 9 did not understand the blur detection task or were uncooperative; 2 had amblyopia, 1 had astigmatism > 1.25 D, and 1 was born < 32 weeks gestation). In total, 49 subjects between the ages of 3 and < 10 years and 10 adult subjects between the ages of 23 and < 32 years met inclusion criteria and were included in the analysis for the blur detection task and 20 subjects > 6 and < 10 years and 10 adults were able to complete the DOF experiment. A summary of subject participation is found in Appendix B. Summary characteristics of age, refractive error, blur threshold, RMS and DOF are found in Table 3.1.

TABLE 3.1 Descriptive and summary statistics for children and adult subjects. Significant differences (two sample t-test) are shown in bold. (* The RMS values reported under the depth-of-field experiment represent RMS values obtained during the blur detection task from the subjects who participated in the depth-of-field experiment.)

		Children	Adults	p-value
		Mean ± Std. Dev. ***n* = 49**	**Mean ± Std. Dev.** ***n* = 10**	
Subject Characteristics	**Age (years)**	6.28±1.62	25.28±2.44	
	SE Refractive Error (D)	+1.63±1.18	+0.82±0.40	**<0.001**
	Astigmatism (D)	-0.57±0.23	-0.40±0.18	**0.02**
Blur Detection Threshold Experiment	**All subjects**	***n* = 49**	***n* = 10**	
	Blur Threshold (arcmin)	1.44±0.46	0.74±0.07	**<0.001**
	RMS (D)	0.32±0.11	0.23±0.05	**<0.001**
	Similar Range Refractive Error	***n* = 27**	***n* = 10**	
	Blur Threshold (arcmin)	1.32±0.47	0.74±0.07	**<0.001**
	RMS (D)	0.29±0.11	0.23±0.05	**0.02**
Depth of Field Experiment	**All subjects**	***n* = 20**	***n* = 10**	
	Depth-of-Field (D)	1.88±0.55	0.93±0.53	**<0.001**
	RMS (D)*	0.30±0.10	0.23±0.05	**0.009**
	Accommodative Criterion	***n* = 13**	***n* = 9**	
	Depth-of-Field (D)	1.70±0.49	0.91±0.56	**0.004**
	RMS (D)*	0.30±0.11	0.22±0.05	**0.048**

3.3.1 Refractive Error Comparisons between Children and Adults

Refractive error analyses revealed a significant, negative correlation between SE and age (n = 49, r = -0.32, p = 0.03) in the children. When comparing the children to the adults, the children had significantly higher mean SE (+1.63 ± 1.18 D vs. +0.82 ± 0.40 D, p < 0.001) and significantly higher astigmatism (-0.57 ± 0.23 D vs. -0.40 ± 0.18 D, p = 0.02) than the adults (Table 3.1).

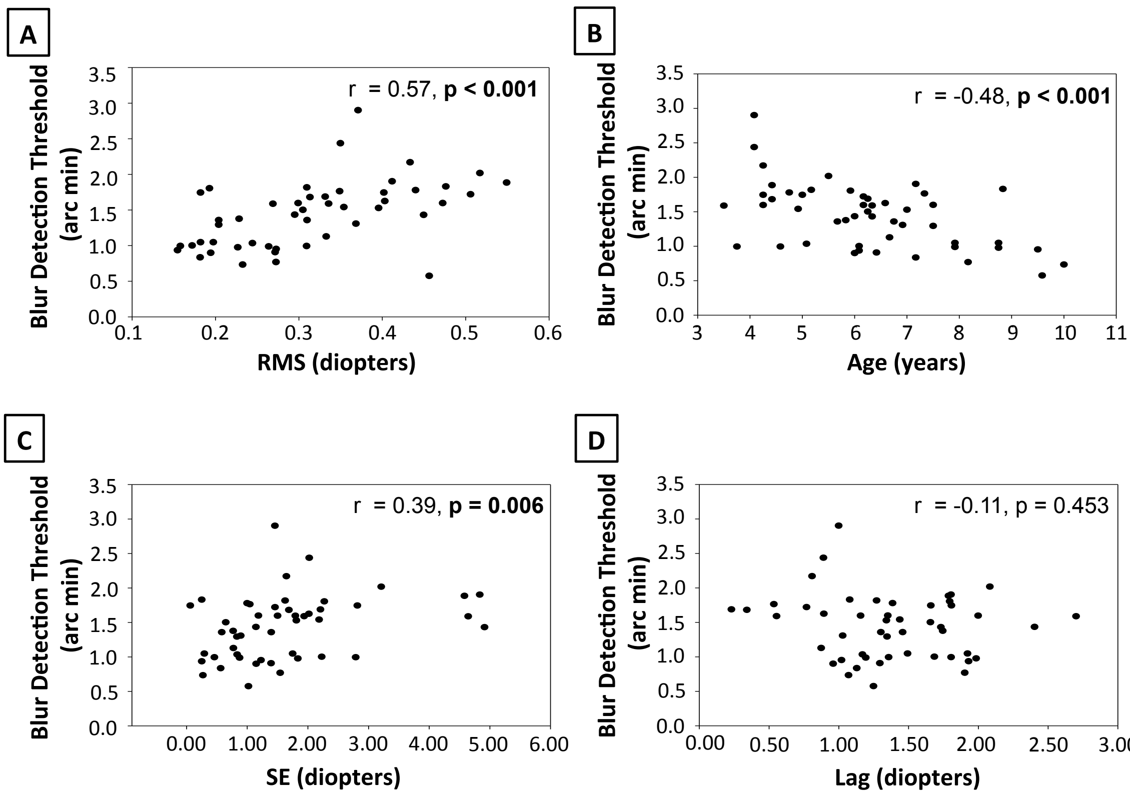
3.3.2 Blur Detection Threshold Comparisons between Children and Adults

The group mean for the blur thresholds were compared between the children and adults. Seven of the ten adult subjects identified at least 80% correct on all blur levels tested, making their blur threshold levels too good to measure using the stimuli generated for this experiment. Thus, for comparison purposes, those seven adults were assigned a threshold value of 0.71, equivalent to the lowest level of convolved blur on the chart, representing a conservative estimate of the thresholds for those subjects. The blur threshold of children (n = 49) was significantly larger (p < 0.001) than that of the adults (n = 10). To ensure that the difference between the children and adults was not due to the higher levels of uncorrected hyperopia in the children, the analysis was repeated with children who had similar refractive errors to the refractive error range of the adult subjects (< +1.51 D SE). Even with similar range of SE, the children (n = 27) still had higher blur detection thresholds than the adults (children 1.32', adults 0.74', p < 0.001). As with SE, during the blur detection task, RMS was also significantly higher in children (n = 49) than adults (n = 10) (p < 0.001) when comparing all children (p < 0.001) or when comparing the subset of children (*n* = 27) with a similar range of refractive error as the adults ($p = 0.02$) (Table 3.1).

3.3.3 Blur Detection Threshold and its Associations with RMS, SE, Age and Accommodative Lag

Spearman correlations revealed that RMS (Figure 3.3a, $r = 0.58$, $p < 0.001$), age (Figure 3.3c, $r = -0.48$, $p < 0.001$), and SE (Figure 3.3b, $r = 0.39$, $p = 0.006$) were each significantly associated with blur detection thresholds in children. Significant associations between blur detection thresholds and accommodative lag was not detected (Figure 3.3d, $r = -0.11$, $p = 0.453$).

FIGURE 3.3 Blur detection thresholds as a function of (A) RMS, (B) age, (C) most plus spherical equivalent refractive error, and (D) accommodative lag in children (n = 49) aged 3 to < 10 years.



Next, multivariable regression analysis was performed to assess the relationship between blur detection thresholds and independent variables RMS, age, SE and accommodative lag. Both unadjusted (univariable regression – for comparison purposes) and adjusted (multivariable regression) results are presented in Table 3.2. As expected, based on the Spearman rank correlations, blur detection thresholds were significantly associated with RMS ($p < 0.001$), age ($p < 0.001$) and SE ($p = 0.023$) in the unadjusted univariable analysis. Blur detection thresholds were found to be significantly associated with RMS ($p = 0.001$) and age ($p < 0.001$) in the adjusted multivariable analysis.

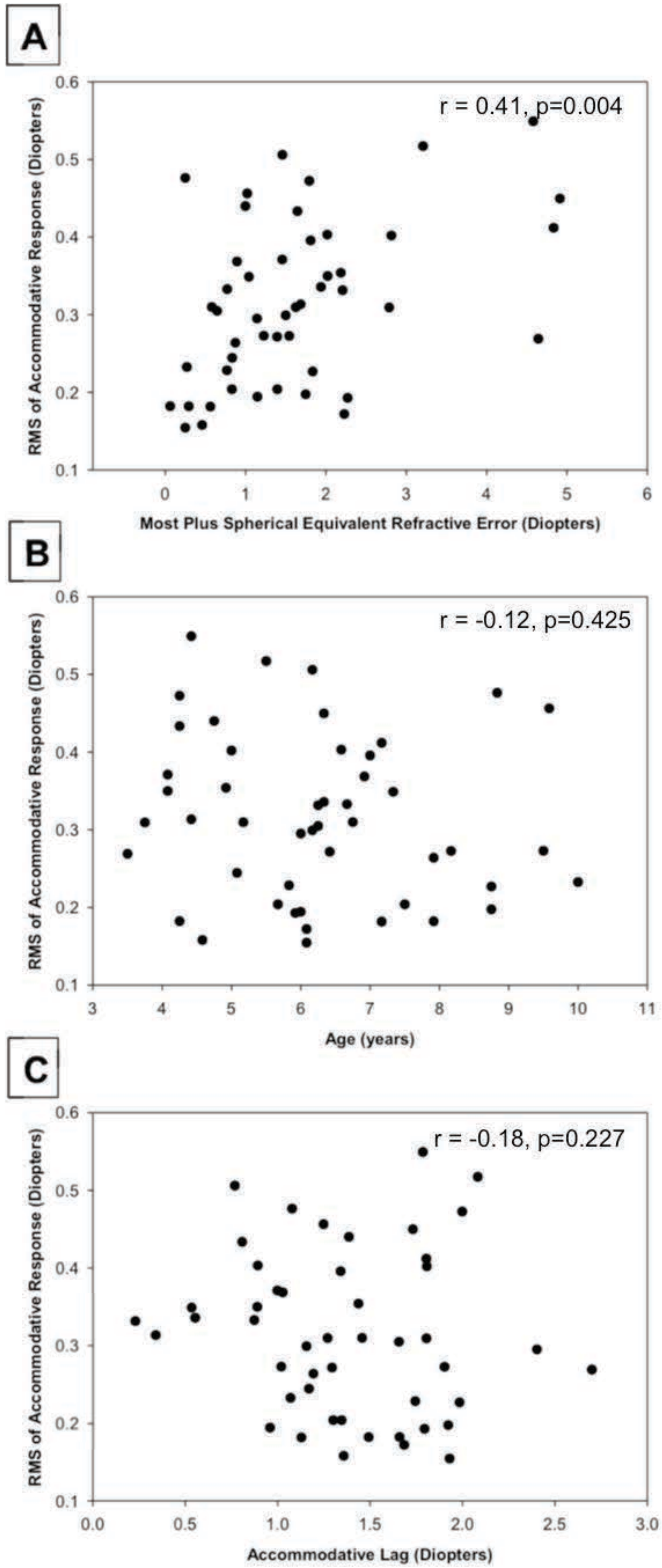
TABLE 3.2 Unadjusted (univariable) and adjusted (multivariable) linear regression for outcome blur threshold, and independent variables for accommodative variability (RMS), age, uncorrected hyperopia (SE) and accommodative lag. Significance (< 0.05) values are in bold.

	Unadjusted			Adjusted		
	Beta-coeff	**95% CI**	**p-value**	**Beta-coeff**	**95% CI**	**p-value**
Intercept	-	-	-	1.91	1.27 to 2.54	**<0.001**
RMS	2.34	1.24 to 3.45	**<0.001**	1.86	0.77 to 2.94	**0.001**
Age	-0.15	-0.22 to -0.08	**<0.001**	-0.14	-0.20 to -0.08	**<0.001**
SE	0.13	0.02 to 0.24	**0.023**	0.02	-0.09 to 0.12	0.726
Lag	-0.13	-0.39 to 0.13	0.329	-0.15	-0.37 to 0.06	0.151

3.3.4 RMS and its Associations with SE, Age and Accommodative Lag

Spearman correlations revealed that SE (Figure 3.4a, r = 0.41, p = 0.004) was significantly associated with RMS. A significant association was not detected between age and RMS (Figure 3.4b, r = -0.12, p = 0.425), or accommodative lag (Figure 3.4c, r = -0.18, p = 0.227) and RMS in this sample population.

FIGURE 3.4 Accommodative variability (RMS) as a function of (A) most plus spherical equivalent, (B) age, and (C) accommodative lag in children (n = 49) aged 3 to < 10 years.



Next, multivariable regression analysis was performed to assess the relationship between RMS and independent variables SE, age and accommodative lag. Both unadjusted (univariable regression – for comparison purposes) and adjusted (multivariable regression) results are presented in Table 3.3. As expected, based on the Spearman rank correlations, a significant association was only detected between RMS and SE ($p = 0.002$) in the unadjusted univariable analysis. In the adjusted multivariable model RMS was found to be significantly associated with SE ($p < 0.001$) and accommodative lag ($p = 0.035$).

The original analysis did not require a minimum number of data points per bin for analysis. Thus, to ensure that bins with missing data did not impact the results, the data were re-analyzed while excluding bins that were missing ≥ 60% of possible data points (missing ≥ 150 data points of possible 250). Despite small changes in the beta-coefficients the general trends and significance remained unchanged for all models that included RMS as either the independent or dependent variable.

TABLE 3.3 Unadjusted (univariable) and adjusted (multivariable) linear regression for outcome RMS, and independent variables age, uncorrected hyperopia (SE) and accommodative lag. Significant p-values (< 0.05) values are in bold.

	Unadjusted			**Adjusted**		
	Beta-coeff	**95% CI**	**p-value**	**Beta-coeff**	**95% CI**	**p-value**
Intercept	-	-	-	0.32	0.18 to 0.47	**<0.001**
Age	-0.01	-0.03 to 0.01	**0.327**	-0.001	-0.02 to 0.02	0.942
SE	0.04	0.02 to 0.06	**0.002**	0.05	0.02 to 0.07	**<0.001**
Lag	-0.02	-0.08 to 0.04	0.455	-0.06	-0.12 to -0.005	**0.035**

3.3.4 Depth-of-Field Experiment

The DOF measures were evaluated to determine whether children had larger DOF than adults. The results are found in Table 3.1. Twenty of the 31 children between the ages of 6 and < 10 years and all 10 adult subjects were able to complete the DOF experiment. The mean DOF of the children (*n* = 20, mean = 1.88 ± 0.55 D) was significantly larger (*p* < 0.001) than that of the adults (*n* = 10, mean = 0.93 ± 0.53 D). Next, RMS obtained during the blur detection task was compared between the children and the adults who were included in the DOF experiment. The RMS of the children (*n* = 20, mean = 0.30 ± 0.10 D) was significantly larger (*p* = 0.009) than the adults (*n* = 10, mean = 0.23 ± 0.05 D). Because the subjects were not cyclopleged during the experiment, the analyses were repeated on a subset of subjects whose average of the five proximal and average of the five distal measures of DOF were within 0.75 D of one another to increase the likelihood that the subjects were repeatedly accommodating to the same place in space for both conditions during testing. The average DOF for this subset of children (*n* = 13, mean = 1.70 ± 0.49 D) was significantly larger (*p* = 0.004) than the adults (*n* = 9, mean = 0.91 ± 0.56 D). Even in the smaller subset of subjects, there was still a significant difference in RMS (*p* = 0.048) between the children (*n* = 13, mean = 0.30 ± 0.11 D) and the adults (*n* = 9, mean = 0.22 ± 0.05 D).

Because DOF is highly influenced by pupil size, the mean pupil sizes collected by the PR during each of the DOF measures were compared between the children and adults for both the proximal and distal conditions. There was no significant difference in pupil size between the children (*n* = 20) and adults (*n* = 10) when determining the proximal edge of the DOF (6.4± 0.7 mm vs. 5.9 ± 0.5 mm, *p* = 0.08). In the distal condition, the mean pupil size for the children (n = 19, one child did not have PR data available) was significantly larger than that of the adults (n = 10) (6.6 ± 0.5 mm vs. 5.7 ± 0.7 mm, $p < 0.001$). The mean pupil size was also compared using only the subset of children who met the accommodative repeatability criteria described above. A significant difference was still not detected in the proximal condition between the two groups (6.5 ± 0.7 mm vs. 5.9 ± 0.5 mm, $p = 0.07$), however, the adults had significantly smaller pupils than the subset of children in the distal condition (6.6 ± 0.5 mm vs. 5.7 ± 0.7 mm, $p = 0.004$).

3.4 Discussion

The children in this study had higher blur detection thresholds, larger RMS and larger DOF than the adult subjects. Increased RMS and younger age were found to be independently associated with increased blur detection thresholds in multivariable analysis when adjusting for SE and accommodative lag. Additionally, SE and accommodative lag were found to be independently associated with RMS when adjusted for age.

It has been shown in adult subjects that microfluctuations act as sub-threshold blur detectors, as the magnitude of the microfluctuations are less than the DOF in the same eyes (Kotulak and Schor 1986). The same relationship was found in the present study in both the children and the adult control subjects, as the microfluctuations for each participant was less than their measured DOF as shown in Table 3.1. (note: RMS value reported in the table should be doubled when comparing to the DOF given that the entire range of the DOF is reported). In the blur detection threshold experiment, the majority of adults were able to distinguish the clear letter from the blurred letters for all levels of blur tested (most adults did not reach their threshold) as opposed to the children, who on average, were unable to distinguish between the clear letter and 1.41 arc minutes of added blur (approximately the 3rd smallest level of convolved blur). These differences in blur detection were not due to the children having larger amounts of uncorrected refractive error, as the difference remained significant when children with refractive errors within the same range as the adult subjects were compared. It is unknown if the discrepancies between the adults and children lie in true biological differences, behavioral differences, or a combination of the two. In the blur threshold experiment, three children (two 9 and one 8 year-old) had lower blur detection thresholds than the adult with the highest true threshold, suggesting that adult-like blur thresholds are possible in some older children, but adult-like thresholds are the exception as all of the other children had higher blur detection thresholds than the adults.

With regards to the DOF experiment, it is clear that the DOF experiment itself was difficult for the children as only ~2/3 of the children (n = 20) were able to complete the experiment and only 65% of those children (n = 13) met the imposed accommodative repeatability criteria. Thus, while this study offers preliminary insight into DOF in children, the results of the DOF experiment should be viewed with caution given the limited number of children able to perform the task and the limitations of the experimental design, discussed below.

The children in this study had significantly larger DOF than the adults with and without the accommodative repeatability criterion. Given that microfluctuations are thought to be sub-threshold blur detectors, it would be expected that the RMS in children would be larger than those of the adults since they also had larger ranges of DOF. When comparing RMS values as measured in the blur detection experiment between all children and adults who had participated in the DOF experiment, the children had significantly larger RMS values. Of the 20 children who were included in the analysis, 7 of them did not meet the accommodative repeatability criterion. It is interesting to note that all but one of the children who did not meet the accommodative repeatability criteria had the largest DOFs (bottom half of the DOF distribution). The lack of children (n = 7) meeting the accommodative repeatability could be secondary to the children not understanding the task, or that those children do indeed have larger DOF and their accommodation varied within that range during the experiment resulting in more variable accommodative responses between trials. Once applying the accommodative repeatability criterion, the children still had significantly larger RMS values than the adults (p = 0.048). Thus, our results are in agreement with other studies reporting that RMS and DOF are related (Kotulak and Schor 1986, Yao, Lin et al. 2010), however additional insight into the relationships between RMS and DOF in children will require further investigation with a larger number of subjects. Additionally, it is important to note that the range of DOF cannot be directly compared to the accommodative microfluctuations of the blur detection task in this study as the two experimental methodologies differed by the task itself as well as the stimulus and stimulus size and the eye in which the measures were obtained (blur detection threshold: most plus eye; DOF: right eye). However, in the children who completed the DOF task (n = 20), a significant difference (p = 0.313) in RMS was not detected between the most plus and least plus eyes (data not shown) and thus using different eyes for the analysis is unlikely to affect the results.

While this study has shown that higher levels of blur detection thresholds among children are associated with both higher magnitudes of RMS and younger age, SE and accommodative lag were not found to be independently associated with blur detection thresholds in the adjusted multivariable analysis using blur detection thresholds as the outcome (Table 3.2). However, increased SE and decreased accommodative lag were independently associated with RMS in the adjusted multivariable analysis using RMS as the outcome (Table 3.3). Thus, while SE was not independently associated with blur detection thresholds, the association between increased SE and increased RMS suggests that perhaps SE has an effect on blur detection thresholds through RMS. Further work in this area needs to be completed prior to understand the relationship between increased SE and increased RMS and its effect on blur detection thresholds.

It is thought that increased levels of accommodative lag may result in increased defocus, which could impact one's ability to detect blur (Valeshabad 2015). However, the magnitude of the accommodative lag is not always associated with increased levels of perceived blur (Sreenivasan, Aslakson et al. 2013, Roberts, Anderson et al. 2015), which may explain why blur detection thresholds were not associated with accommodative lag in this study even without controlling for other confounding variables (Figure 3.3). Accommodative lag was however found to be independently associated with RMS. The negative beta-coefficient suggests that once the effect of age and SE are adjusted for, as accommodative lag increases, RMS decreases. This would be supportive of the motor theory discussed in Chapter 2.

While this study has shown that higher levels of blur detection thresholds among children are associated with both higher magnitudes of RMS and younger age, it is unknown whether the associations are due to immaturities in the young visual system or the significant associations are secondary to neural deficits regarding blur detection. It is not surprising that blur detection thresholds decreased with age as the young behavioral visual system (i.e.: contrast sensitivity) continues to mature up to 8 years and above (Bradley and Freeman 1982). However, RMS remained independently associated with blur detection thresholds when adjusting for age in this sample population ($p < 0.001$), suggesting that some children have increased blur detection levels that are unrelated to visual immaturities due to age.

3.4.1 Study Limitations

There are limitations to the study. One limitation of the study is that only 49 subjects were included in the analysis and there were few subjects with SE > +3.00 SE included in the study. The relatively small sample with high refractive errors constrains the ability to determine the impact of uncorrected hyperopia on blur detection thresholds when adjusting for other factors such as RMS, age and accommodative lag. It is difficult to recruit previously uncorrected subjects with > +3.00 D SE as population based studies in the United States suggest the prevalence of > +3.00 D SE in children 72 months of age or younger is approximately ~10% (Multi-Ethnic Pediatric Eye Disease Study 2010, Wen, Tarczy-Hornoch et al. 2013). Despite the low number of subjects in the study with > +3.00 D SE, the magnitude of refractive error was still independently associated with higher RMS.

Another limitation to the study is that neither the blur detection threshold experiment nor the DOF experiment was performed under cycloplegia. Inaccurate accommodation is thought to impact defocus, which is additive to the Gaussian convolution applied to the stimuli (Valeshabad 2015). However, the purpose of the study was to determine if there was an association between blur detection and RMS, age, uncorrected hyperopia, and accommodative lag in children under natural viewing conditions. Additionally, if lag was contributing to the results as a group, it would be expected that the children would have greater accommodative lags than the adults given that the adults have much lower blur thresholds. However, a statistically significant difference in accommodative lag was not detected between the groups (analyses not shown), further suggesting that the magnitude of accommodative lag did not impact the blur detection thresholds in this study.

Given that our study was done without cycloplegia we are unable to differentiate whether the individuals with higher levels of blur detection have neurological deficits in the afferent pathway resulting in decreased ability to detect blur or if their higher thresholds were simply due to noise in the signal due to increased RMS. Further investigation of blur detection thresholds in children under cycloplegia is needed to differentiate the neural blur thresholds from the functional blur thresholds in children given the strong association between accommodative variability and blur detection thresholds in the children in this sample population.

The DOF experiments are also likely to be affected by the lack of cycloplegia. Like blur detection thresholds, the purpose of the DOF study was to determine the individual's DOF in their own habitual viewing state. Not only was accommodation able to fluctuate, but pupil size was able to vary naturally as well. Pupil size was monitored throughout the study and despite the adults having significantly smaller pupils in the distal condition; pupil size was within 1 mm, on average, across the two groups. Also, a difference in pupil size was unlikely to be influential in the results, as the adults' smaller pupils would have resulted in an expected larger DOF (Atchison, Fisher et al. 2005) but the adults had smaller DOF than the children Additionally, both groups had pupils larger than 4 mm, where pupil size is reported to have little impact on measures of DOF (Atchison, Fisher et al. 2005). To account for variability of the accuracy of the accommodative response, DOF analysis was first performed using all subjects and then repeated imposing an accommodative repeatability criterion. The over-all results did not change with or without the criterion in that the children still had significantly larger DOF than the adults. The adult measures of DOF were similar to other DOF measures found in other studies (Campbell 1957, Atchison, Fisher et al. 2005) particularly when measuring DOF on an accommodating eye (Bernal-Molina, Montes-Mico et al. 2014). DOF measures have not been explored in children and thus there are no comparative studies.

Another limitation in the DOF experiment is that subjects may have made small saccadic eye movements from the fixating letter to the proximal or distal letter during the experiment. This may have resulted in larger measures of DOF as the subjects would have likely reported the letters were similar in clarity sooner.

3.4.2 Summary

In summary, the results of this study suggest that, as a group, children do not have adult-like blur detection thresholds or DOF by 10 years of age. Increased RMS and younger age are independently associated with greater blur detection thresholds in children aged 3 to < 10 years. Additionally, children with larger amounts of uncorrected hyperopic refractive error have significantly larger magnitudes of accommodative microfluctuations, which are significantly associated with increased blur detection thresholds.

CHAPTER 4: Accommodative Behavior of Young Uncorrected Hyperopes during Sustained Viewing of a Passive and Active Task

4.1 Introduction

Retinal image quality is often at the forefront of discussions of visual experience. The accuracy of accommodation is a common measure of defocus in children, which in turn is used to infer retinal image quality (Candy, Gray et al. 2012). Decreased image quality is often times considered in the context of amblyopia and strabismus as children with moderate and high amounts of uncorrected hyperopia are at higher risk for developing such anomalies (Ingram, Arnold et al. 1990, Ingram, Gill et al. 1994, Ingram, Gill et al. 2000, Fawcett and Birch 2003). There is little debate that young hyperopes with amblyopia or strabismus need to be given optical correction to alleviate part or all of their accommodative demand (American Optometric Association 2004, American Academy of Ophthalmology 2012). However, areas of clinical uncertainty remain as to the most appropriate treatment strategies for young hyperopic children in the absence of amblyopia and strabismus.

There are currently no evidence-based prescribing guidelines for young hyperopic children but rather only consensus-based guidelines (Miller and Harvey 1998, Lyons, Jones et al. 2004). The current consensus-based prescribing guidelines for hyperopia are driven by a practitioner's clinical experience, often times with the primary aim of preventing amblyopia and strabismus. However, cross-sectional population based studies in the United States have shown that > 80% of children aged 3 to < 6 years with > +3.50 D spherical equivalent (SE) hyperopia did not have amblyopia or strabismus at the time of the study (Tarczy-Hornoch, Varma et al. 2011). Nevertheless, the absence of amblyopia or strabismus does not necessarily equate to those children having normal visual experience.

Several studies have shown that infants and children with larger amounts of hyperopia tend to under-accommodate when viewing a near stimulus relative to children with lesser amounts of hyperopia (Ingram, Gill et al. 1994, Mutti 2007, Horwood and Riddell 2011, Candy, Gray et al. 2012, Tarczy-Hornoch 2012). While the above studies have shown that children with uncorrected hyperopia tend to under-accommodative to a near stimulus, the accommodative measures were taken over a short period of time and discussed in the context of the mean accommodative response. However, the accommodative response is not static but instead fluctuates around the mean accommodative response at a rate < 3 Hz (Campbell, Westheimer et al. 1958). The fluctuations are referred to as accommodative microfluctuations and the magnitude of the fluctuations are a measure of the stability of the accommodative response.

Microfluctuations measured in the time domain are calculated as the root mean square (RMS) of the accommodative response (Gray, Winn et al. 1993) and is a representative measure of the overall accommodative variability during the time in which the response was measured. Microfluctuations are also characterized in the frequency domain using power spectra analysis. Power spectral analysis of the accommodative response has shown that accommodation primarily has activity in the low frequency component (LFC, 0-0.6 Hz) and high frequency component (HFC, 1–2.3 Hz) of the signal (Winn, Pugh et al. 1990, Harb, Thorn et al. 2006). The LFC component of the accommodative response is thought to play an integral role in the accommodative control system (Charman and Heron 1988), given that the HFC has been shown to be correlated with arterial pulse (Winn, Pugh et al. 1990). Subjects with increased amounts of uncorrected hyperopia may be particularly susceptible to increased energy in the LFC of the power spectrum of the accommodative response if they allow their accommodation to drift in and out of focus (Horwood and Riddell 2011).

As with accommodative lag, fluctuations of the accommodative response may also impact retinal image quality if the fluctuations extend outside of the depth-of-focus. Currently the stability of the accommodative response beyond a thirty-second period of time (Schultz, Sinnott et al. 2009) is unknown in children, yet it is of particular concern during the school day while performing near activities and while completing homework outside of school. Additionally, little is known about the effect of hyperopic refractive error on accommodative stability as individuals with hyperopia have a greater accommodative demand at all viewing distances than individuals with emmetropia or myopia. Previous studies have demonstrated that accommodative lag and accommodative microfluctuations increase with increasing accommodative demands (Kotulak and Schor 1986, Candy and Bharadwaj 2007, Anderson, Glasser et al. 2010). We made the same observation in Chapter 2 when comparing the change in accommodative behavior between the stimuli at 100 cm (1 D demand) versus 33 cm (3 D demand) (Figure 2.2). Based on those observations, one might expect children with uncorrected hyperopia to not only have larger accommodative lags but also have larger accommodative microfluctuations relative to similar aged children with lesser amounts of hyperopia. In fact, in Chapter 3, during the blur detection task, increased uncorrected hyperopia was associated with an increase in RMS (Figure 3.4).

An additional confounding variable that is known to impact the accommodative response is the cognitive demand of an accommodative task. Most studies of accommodative accuracy and accommodative microfluctuations consist of the subject fixating a detailed picture stimulus (Horwood and Riddell 2011, Candy, Gray et al. 2012), cartoon movie (Candy and Bharadwaj 2007, Anderson, Glasser et al. 2010) or Maltese cross (Schultz, Sinnott et al. 2009), which all contain a wide spatial frequency distribution. However, the accommodative response has been shown to increase under testing conditions that require greater cognitive effort despite the stimulus itself being unchanged (Bullimore and Gilmartin 1988, Woodhouse, Cregg et al. 2000, Francis, Jiang et al. 2003). The effect of cognitive effort on accommodative stability has yet to be studied. However, if accommodative stability increases with an increased lag of accommodation while viewing a similar stimulus as we found in Chapter 2 (Figure 2.2: blur+disparity versus blur-only at 33 cm) then it may be expected that if the accommodative response is more accurate (i.e.: smaller lag of accommodation) during a task that requires increased cognitive effort, the accommodative response would likely be less variable as well.

The purpose of this study was to investigate accommodative lag and accommodative variability in young hyperopes between the ages of 3 and < 10 years over a longer duration of time than previously studied and during tasks varying in cognitive demands. First, we sought to determine the effect of cognition on accommodative lag and accommodative variability by comparing the accommodative responses during a passive viewing task versus an active viewing task. Secondly, the magnitudes of accommodative lag and RMS were evaluated under each viewing condition to determine if the children in this study with larger amounts of uncorrected hyperopia also had increased accommodative lag or increased accommodative variability compared to children with lesser amounts of hyperopia. Lastly, because the accommodative behavior beyond a 30 second period is unknown in children, we sought to determine if children experienced a change in the mean accommodative response or variability throughout the duration of the experiment and if so, whether children with greater amounts of hyperopia demonstrated the greatest changes. Adults were also recruited to act as comparative control subjects with mature visual systems.

4.2 Methods

4.2.1 Study Subjects

Subjects aged 3 to < 10 years and non-presbyopic adult subjects were recruited from the University of Houston College of Optometry staff, student, and patient populations, as well as the local community. The study followed the tenets of the Declaration of Helsinki and was approved by the University's institutional review board for the protection of human subjects. All subjects over the age of 18 years provided written informed consent and subjects younger than 18 years provided assent while their parents provided written parental permission to participate in the study.

Prior to participation in the study, subjects or their parents (in the case of child participants) were queried to ensure subjects met the inclusion criteria of ≥ 32 weeks gestation and a birth weight ≥ 2500 grams. Subjects were also screened for the presence of exclusion criteria: history of ocular or systemic diagnoses that may impact accommodation, were taking medications known to impact accommodation, or had a history of developmental delays or behavioral diagnoses, such as attention deficit disorders. Subjects were also ineligible from participation if they had a current or previous refractive error correction or had known cycloplegic refractive error ≤ -0.50 diopters (D) spherical equivalent (SE), anisometropia > 1.00 D SE or astigmatism > 1.25 D cylinder.

In addition to participating in the experiment, all subjects had a complete vision examination performed by the investigator. The vision examination included monocular visual acuity with isolated letters surrounded by crowding bars (top, bottom, left and right positioned at one letter width from the letter) following the electronic psychometric visual acuity testing protocol established by the Pediatric Eye Disease Investigator Group (electronic HOTV (Holmes, Beck et al. 2001, Moke, Turpin et al. 2001) for subjects < 8 years and ETDRS (Beck, Moke et al. 2003) for subjects ≥8 years presented on the M&S SmartSystem (M&S Technologies, Inc. Niles, IL) calibrated for testing at 14.5 feet. In addition to visual acuity testing, unilateral cover test was performed to rule-out strabismus. Subjects were excluded from data analysis if they did not have typical visual acuity for their age (< 20/50 for 3 to < 4 years, < 20/40 for 4 to < 5 years, < 20/32 for 5 to < 6 years (Pan, Tarczy-Hornoch et al. 2009), 20/25 or worse for subjects 6 years and older (Scheiman, Hertle et al. 2008) or were diagnosed with strabismus (any movement seen on unilateral cover test) or amblyopia (visual acuity > 2 lines intraocular difference) (Pediatric Eye Disease Investigator 2002).

Subjects also had a cycloplegic assessment of refractive error using the Grand Seiko WAM-5500® open-field auto-refractor (RyuSyo Industrial Co., Ltd. Hiroshima, Japan), and a dilated fundus examination to rule out ocular pathology. Three measures of cycloplegic refractive error were obtained for each eye (30 minutes after instillation of 1% cyclopentolate). Each of the three measures were transformed into power vector notation, which represents the original sphero-cylinder refractive error as three powered lenses: a spherical lens power M (i.e.: spherical equivalent), and two Jackson Cross Cylinder lenses, one with power J_0 at axis 0° and the other with power J_{45} at axis 45° (Thibos, Wheeler et al. 1997). Once each of the cycloplegic measures were transformed into power vector notation, the three respective values for each vector were averaged, then the three average vectors were back-transformed to represent the mean sphero-cylinder cycloplegic refractive error for the right and left eye of each subject. The mean SE value (i.e.: mean M vector) was used to classify the refractive error of each eye as the most plus and least plus eye of each subject.

Power refraction was the technique used to dynamically record accommodative responses during experimental conditions and only provides measures of refraction in the vertical meridian (described in further detail below). Thus, the back-transformed mean refractive error obtained from cycloplegic autorefraction in sphero-cylinder form was used to calculate the power in the vertical meridian (090) of the eye (described below) in order to combine the cycloplegic auto-refraction and power refraction measures within each subject to calculate the total accommodative response of the subject (described in detail in the data analysis section).

The vertical meridian of each eye, as measured by auto-refraction, was calculated as follows:

$$Power\ in\ Vertical\ Meridian = S + Csin^2(90 - \alpha)$$

where *S* is the spherical power, *C* is the cylindrical power, *α* is the axis, and *90* represents the desired vertical meridian.

For children who were recruited from the optometry clinic, eligibility was known prior to the consent process, as the clinicians who referred the patient to the study were aware of the study inclusion/exclusion criteria. However, children recruited outside of the optometry clinic were queried and screened for the exclusion criteria regarding previous diagnoses and medications prior to the laboratory visit while the refractive error exclusion criteria and other vision examination criteria (described below) was determined at the vision examination, which occurred after the laboratory visit. Children identified during the vision examination to be ineligible were not included in the analysis.

4.2.2 Experimental Set-up

For each experimental condition subjects viewed shapes (squares, circles, triangles, stars and arrows) or letters that subtended 0.21° in the vertical dimension (for the letter stimuli the size was based on lower case letters such “a” and “s”). The stimuli were displayed on an iPad Air® (Apple Inc., Cupertino, CA) (2048 x 1536 pixels) at 33 cm using Keynote® (Apple Inc., Cupertino, CA) presentation software in a viewing window subtending a total stimulus area of 8.9 cm (15.09º) horizontally (~7.55º to the left and right of center) and 4.6 cm (7.94º) vertically (~4º above and below center) for the reading passages (described below) and 4.15 cm (7.20º) horizontally and 2.2 cm (3.8º) vertically for the shape stimuli (described below). The viewing area was decreased for the shapes stimuli because the blank white screen of the larger viewing area resulted in pupil constriction below 4 mm, which has been shown to affect the accuracy of the refractive error measures of the PR (Gekeler, Schaeffel et al. 1997, Choi, Weiss et al. 2000). The iPad Air® was positioned above a beam-splitter (passes infrared light, reflects visible light), which allowed the stimulus to be projected directly in front of the subject (99.7% Weber contrast through the beam splitter) at an optical viewing distance of 33 cm (3 D demand). A photorefractor was located one meter in front of the subject (67 cm behind the stimulus image) allowing for continuous measures of refractive error, eye position and pupil size (as described below) throughout the experiments. The stimulus apparatus as well as the photorefractor were covered using a curtain enclosure throughout the experimental testing conditions and the room lights were dimmed to limit any distractions and aid in photorefraction measurement capture. The subjects were positioned in a headrest throughout the experiments to limit head movements.

4.2.3 Active Viewing Experiment

For the active viewing experiment, subjects performed a cognitively active task (reading story passages or answering questions about displayed shapes) for ten consecutive minutes. Prior to experimental testing, children 6 to < 10 years participated in a screening evaluation to determine each individual subject's independent reading level using the San Diego Quick Assessment test (La Pray M. 1969). In brief, the quick assessment consists of thirteen words from each grade level; pre-primer to eleventh grade. The subjects were instructed to read each consecutive word beginning at the pre-primer level until the subject missed more than one word at one level. The last level at which the subject missed one word or less was considered the subject's independent reading level. Subjects who were capable of reading at the kindergarten level or above read story passages aloud during the active viewing condition at their own individual reading level as defined by the San Diego Quick Assessment test. Multiple passages from each grade level were obtained from AIMSWEB® (Pearson Inc. London, England) and were compiled into individual Keynote® (slide presentation software for Apple® products) presentations and displayed on the iPad Air®. The reading passages were centered in the display area. At the end of each passage the child answered a multiple-choice question related to the passage to encourage the child to actively attend to the passages throughout the experiment. The investigator followed along while the child read the passages and advanced each slide throughout the experiment using an iPhone® (Apple Inc. Cupertino, CA). The adult subjects read from a Master's Thesis on the topic of economics. Rather than answering questions throughout the passage, the adults were informed prior to testing that they would be asked questions regarding the passage at the end of the 10-minute testing period. The subjects were informed of the impending questions to encourage the adults to actively attend to the passage throughout the experiment. The adults read aloud and when they reached the end of the slide, they informed the investigator and the investigator advanced the slide.

All subjects < 6 years as well as subjects ≥ 6 years who were unable to read the kindergarten screening words of the San Diego Quick Assessment viewed the shape stimuli. The shapes were displayed using a pre-programmed slide presentation made in Keynote®. Each slide had 1 to 5 shapes displayed at one time with a display time equal to 2 seconds per shape with the exception that when 5 shapes were displayed, the slide was shown for 9 seconds. The shapes were displayed in the center of the viewing area and were evenly spaced with a total stimulus width of 4.4º horizontally and 0.21º vertically. Throughout the trial, the investigator asked the subject questions about each slide they saw ranging in difficulty from simply naming the shapes, to counting a particular shape, or, for older children in the group, answering questions regarding the spatial distribution of the shapes relative to one another (first, last, before, after). The level of difficulty of the questions asked varied based upon each individual subject's ability to understand and answer the questions.

4.2.4 Passive Viewing Experiment

For the passive viewing experiment, subjects looked at letters or shapes for ten consecutive minutes. For subjects who were presented with shapes during the active viewing task, the same shape stimuli presentation was shown in the passive viewing condition. However the subjects viewed silently and were not asked any questions during the passive viewing condition. The subjects were instructed to look at the shapes and if they looked away, they were reminded to continue looking at the shapes. Subjects ≥ 6 years who read at the kindergarten level or higher on the San Diego Quick Assessment and the adults viewed random letters arranged in rows in a separate Keynote® presentation. The subjects were instructed to look at each letter on the slide beginning at the upper left as though they were reading. Once they looked at all the letters on each slide they were told to inform the investigator who would then advance the slide.

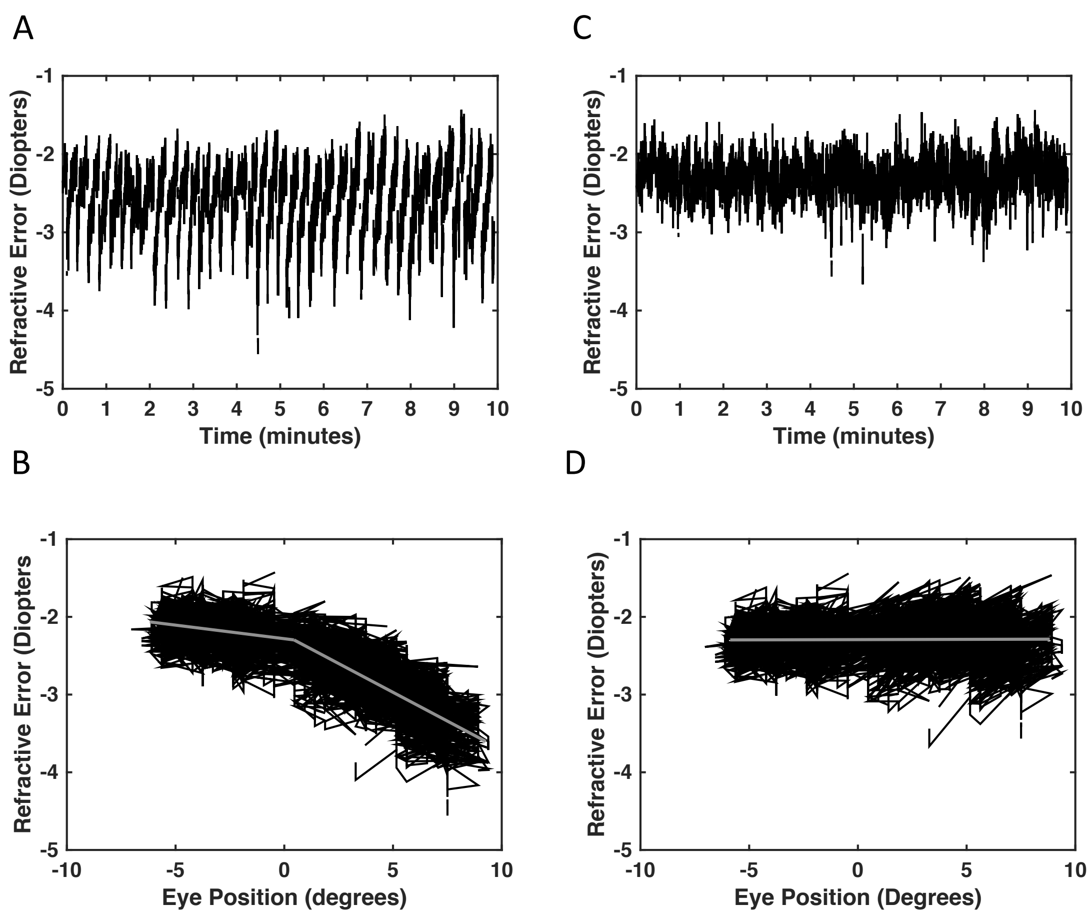
4.2.5 Measures of Accommodation, Eye Position and Pupil Size

Changes in refractive error, eye alignment and pupil size were measured in both eyes during the passive and active viewing conditions using the PowerRef II (PR). The method of eccentric photorefraction has been described in detail elsewhere (Schaeffel, Wilhelm et al. 1993, Gekeler, Schaeffel et al. 1997, Choi, Weiss et al. 2000) and in Appendix A. Prior to experimental testing, each individual underwent a trial lens calibration for each eye to obtain more precise measures of refractive error, described in detail in Appendix A.

Photorefraction data were filtered offline to eliminate outlying data points that are known to be outside of the working range of the PR or points that are unlikely to be physiological in nature (i.e.: large fluctuations secondary to a blink). Measures of refractive error were removed if the change in focus between two data points were > 10 D/second (Harb, Thorn et al. 2006), refractive error measures were < -6.00 D or > +4.00 D (Gekeler, Schaeffel et al. 1997, Choi, Weiss et al. 2000), pupil size was < 4 mm or > 8 mm, and gaze position outside of ± 10° horizontally or ± 5° vertically to eliminate erroneous measures from peripheral refraction (Jennings and Charman 1981, Navarro, Artal et al. 1993) and as recommended by the manufacturer for the first generation PowerRefractor (Plusoptix Inc., Atlanta, GA).

Raw data traces obtained during the reading task and the passive letter task were examined and regular, periodic changes in the refractive error measures were detected. The changes in refractive error were consistent with the dynamic changes in eye position during the task (Figure 4.1a). The effect of eye position was not present for the subjects who viewed the shape stimuli as the shapes were placed in the center of the viewing window and had a much smaller total stimulus width thus requiring small horizontal eye movements. The data with periodic changes in refractive error had a bi-linear distribution with the junction of the two slopes at approximately zero degrees for both the right and left eyes for all subjects (Figure 4.1b). Piecewise linear regression was performed to determine each slope of the refractive error and eye position functions (slope $\leq 0^o$ and slope $> 0^o$). Each eye position datum point was then multiplied by the slope of the respective regression line ($\leq 0^o$ or $> 0^o$) and the product was subtracted from the corresponding refractive error datum point. The correction factor was applied to each eye of each individual subject for each viewing condition (passive and cognitive) for all subjects (children and adults) who viewed the reading passages for the active task or the letters during the passive task prior to any data analysis. The correlation found between eye position and refraction was only apparent when considering horizontal eye movements as there was no correlation between vertical eye alignment and refractive error measures likely due to the smaller vertical component of the viewing window (data not shown). There was also no correlation between pupil size and refractive error measures (data not shown). The effect of the correction factor for horizontal eye position for one adult subject is shown in Figure 4.1c and 4.1d.

FIGURE 4.1 Refractive error and eye position data from the right eye of one adult subject during the cognitive viewing condition. A) Refractive error of the right eye illustrating the periodic changes in the signal throughout the experiment. B) Refractive error plotted as a function of horizontal eye position (degrees). The gray lines represent the change in slope of the data when eye position is ≤ 0° and > 0°. C) Refractive error data plotted as a function of time after the eye position correction factor had been applied to the data. D) Refractive error as a function of eye position after the eye position correction had been applied, illustrating the effectiveness of the correction factor.



4.2.6 Data Analysis

Accommodative lag, total accommodative response, accommodative variability (time and frequency domains), and cycloplegic SE were analyzed in both the passive and active viewing conditions. Accommodative lag was calculated as the difference between the mean refractive error measures obtained by the PR and the 3 D stimulus demand. The total accommodative response was calculated as the difference between the cycloplegic refractive error in the vertical meridian of the right eye obtained from Grand Seiko auto-refraction and the refractive error measures obtained by the PR during the experiment (PR measures the vertical meridian of the eye in dynamic mode). If the subject's far point of the eye is nearer than infinity, the refractive error obtained by the PR has a negative value. For example, if the cycloplegic refractive error in the vertical meridian of the eye was +2.50 D and the refractive error measured during the task was -2.00 D, the total accommodative response would be 4.50D.

Accommodative variability was calculated in both the time and frequency domains from the refractive error data obtained by the PR during each experiment. Accommodative variability in the time domain was calculated using the root mean square (RMS) (Gray, Winn et al. 1993) of the filtered data described above. Accommodative variability in the frequency domain was calculated using the Fast Fourier Transform (FFT) function in Matlab to determine the LFC of the Power Spectrum. The HFC was not analyzed as it is correlated with arterial pulse rather than accommodative function (Winn, Pugh et al. 1990). Prior to running the FFT, missing data points were linearly interpolated and the dc component (i.e.: average response) was then subtracted from the data. The data were then smoothed using a Gaussian function (sigma = 1 standard deviation). The area under the curve of the LFC (0 to 0.6Hz) was used as the outcome measure for the frequency domain. It should be noted that due to the duration of the task, the LFC values will contain energy at frequencies that are lower than previously reported in other studies of accommodative fluctuations (Kotulak and Schor 1986, Gray, Winn et al. 1993, Candy and Bharadwaj 2007, Schultz, Sinnott et al. 2009), given that the lowest frequency is determined by the fundamental frequency (sampling rate/number of data points) and this study recorded responses for substantially longer viewing times than previous studies and thus has substantially more data points than previous studies.

The subjects were divided into two experimental groups and one control group. Group 1 consisted of the children who viewed the shape stimuli and Group 2 the children who read age appropriate reading passages. The control group consisted of the adult subjects.

4.2.7 Accommodative Lag, RMS and LFC Comparisons between Groups and Conditions

Two factor (condition and group) repeated measures analysis of variance (ANOVA) were used to compare the outcomes average accommodative lag, RMS and LFC across the experimental groups (Group1, Group 2), control group (adults) for both the passive and active viewing conditions. The accommodative variability data (RMS and LFC) were not normally distributed and thus the data were transformed (natural log) for the repeated measures ANOVA. *Post-hoc* pairwise comparisons were performed and were adjusted for multiple comparisons using the Holm-Sidek method.

4.2.8 Relationships between SE and Total Accommodative Response with the Outcomes Average Accommodative Lag, RMS and LFC

Correlations and linear regressions were used to analyze the effect of SE (uncorrected hyperopia) on accommodative lag, RMS and LFC in the two experimental groups. Linear regressions were repeated to analyze the effect of total accommodative response on accommodative lag, RMS and LFC. Both SE and total accommodative response were analyzed separately since a relationship between accommodative response and SE would be expected if the children accommodate so as to have equivalent accommodative lags, but not all subjects are likely to have equivalent accommodative responses.

4.2.9 Interaction between SE and Time on the Outcomes Accommodative Lag, RMS and LFC

Random effects mixed linear models were used to analyze the effect of the interaction between refractive error and time on each of the outcomes accommodative lag, RMS and LFC in both the groups of children as well as the control group. Accommodative lag and RMS data were binned in 10-second bins (59 total bins) while LFC components were binned in 1-minute bins to allow for the capture of accommodative drifts in the LFC.

The analysis was repeated by condition using both experimental groups as well as the control group.

The classification of ametropia was based on the most plus eye and thus measures from the most plus eye (as obtained from cycloplegic auto-refraction) were used for all comparisons concerning accommodative measures from the blur detection task as has been done in previous studies of children with uncorrected hyperopia (Rosner and Rosner 1987, Wen, Tarczy-Hornoch et al. 2013). SE was also compared between the children and adults using two-sample t-test. Analysis was performed using Stata® 12.1 (StataCorp 2015) and SigmaPlot 13 (Systat Software, San Jose, CA).

4.4 Results

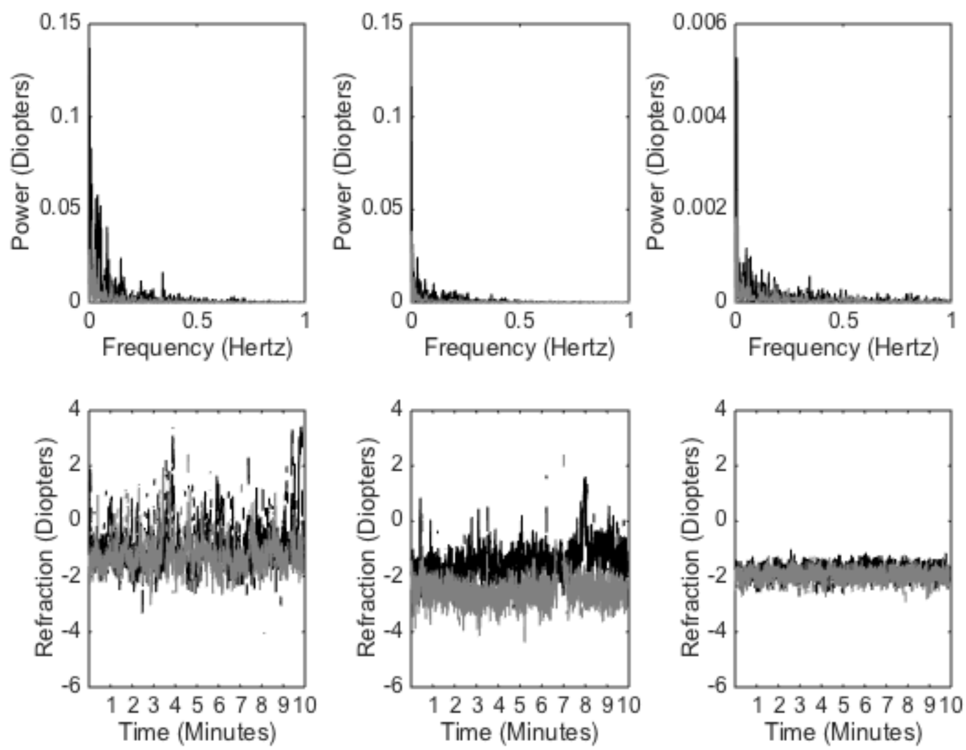
Seventy-four subjects (66 children and 8 adults) were recruited to participate in the study. Of the 66 children, 8 were excluded from data analysis (3 did not have cycloplegic refractive error; 1 did not have a valid calibration for her most plus SE eye; 2 had amblyopia, 1 had astigmatism > 1.25 D, and 1 was born < 32 weeks gestation). Additionally, four subjects were uncooperative for the passive viewing condition (three 3-year olds, one 4-year old) and five different subjects were uncooperative for the active viewing condition (three 3-year-olds, two 4-year-olds). In total, Group 1 included 31 children (24 children were < 6 years and 7 children were ≥ 6 years but unable to read the kindergarten words from the San Diego quick assessment test), Group 2 included 23 children and the Control group included all 8 adult subjects. Descriptive statistics for age, refractive error, accommodative lag, accommodative response and variability (RMS and

LFC) for all groups are found in Table 4.1. Representative examples of subject data traces and coinciding power spectrum analyses for two children with differing refractive errors and one adult are shown in Figure 4.2.

TABLE 4.1 Average descriptive statistics measured over the duration of each experimental condition and within each experimental group. Age, refractive error, accommodative lag and total accommodative response are reported as mean ± *SD*. RMS and LFC are reported as median and interquartile range.

Age Category	Condition	Number of subjects	Variables	Mean/ Median	Std. Dev/IQR
Group 1 (Children Shapes)	Passive	*n* = 31	Age (years)	5.0	±1.0
			Ref Error (D)	+1.79	±1.06
			Accomm Lag (D)	1.72	±0.44
			Total Resp (D)	2.99	±0.87
			RMS (D)	0.57	0.44 to 0.78
			LFC (D^2)	1.25E-03	6.5E-04 to 2.6E-03
	Active	*n* = 27	Age (years)	5.1	±1.1
			Ref Error (D)	+1.70	±1.11
			Accomm Lag (D)	1.47	±0.41
			Total Resp (D)	3.18	±1.00
			RMS (D)	0.32	0.26 to 0.43
			LFC (D^2)	3.40E-04	2.07E-04 to 7.00E-04
Group 2 (Children Text)			Age (years)	7.5	±1.2
			Ref Error (D)	+1.41	±1.24
	Passive	*n* = 23	Accomm Lag (D)	1.34	±0.59
			Total Resp (D)	2.99	±1.32
			RMS (D)	0.36	0.28 to 0.49
			LFC (D^2)	3.56E-04	1.93E-04 to 5.98E-04
	Active		Accomm Lag (D)	1.13	±0.45
			Total Resp (D)	3.20	±1.31
			RMS (D)	0.31	0.23 to 0.31
			LFC (D^2)	2.15E-04	1.01E-04 to 3.02E-04
Group 3 (Adults Text)			Age (years)	25.3	±2.8
			Ref Error (D)	+0.87	±0.44
	Passive	*n* = 8	Accomm Lag (D)	1.12	±0.26
			Total Resp (D)	2.72	±0.57
			RMS (D)	0.24	0.22 to 0.28
			LFC (D^2)	1.27E-04	1.01E-04 to 1.78E-04
	Active		Accomm Lag (D)	1.12	±0.18
			Total Resp (D)	2.72	±0.46
			RMS (D)	0.22	0.17 to 0.24
			LFC (D^2)	7.37E-05	5.56E-05 to 1.12E-04

FIGURE 4.2 Sample data traces (top row) of the most plus eye's accommodative response to the stimulus located at 33 cm (3 D demand) from 3 subjects along with coinciding power spectrum (bottom row) obtained by Fourier analysis. The black traces represent the passive condition while the gray traces represent the active conditions. Note the change in the y-axis scale for the adult subject for the power spectrum analysis.



4.3.1 Summary Characteristics for Cycloplegic Refractive Error and Age

While there was a range of almost +5.00 D of uncorrected SE hyperopia in the children over the ages of 3 to < 10 years, the correlation between refractive error and age did not reach significance across the entire sample of children (n = 57, r = -0.25, p = 0.063, Pearson's correlation). A two-sample t-test revealed that most plus cycloplegic spherical equivalent refractive error in the children (n = 57) was significantly higher than the adults (n = 8) (p = 0.002).

4.3.2 Accommodative lag, RMS and LFC Comparisons between Groups and Conditions

Accommodative behavior was investigated between the passive and active viewing conditions to determine if cognitive effort impacted the accuracy or stability of the accommodative response. Both groups of children (those viewing shapes and those reading passages) had significantly larger mean accommodative lags (Group 1: $p < 0.001$, Group 2: $p = 0.002$) across the 10-minute passive viewing period as compared to the active viewing condition (Table 4.2, Figure 4.3). Coinciding with the larger accommodative lag, and thus lower overall mean response in the passive condition, the accommodative response was significantly more variable as compared to the cognitive condition ($p < 0.001$) for RMS and the LFC for the two groups of children. Unlike the children, the adults did not have a difference in overall mean accommodative lag between the two conditions ($p = 0.990$). However, despite having similar accommodative lags between the two conditions, the accommodative response of the adults was significantly more variable in the passive condition for RMS ($p = 0.030$) and

LFC (p = 0.003), although the difference in median RMS between the two conditions was 0.02 D, which is not likely to be a meaningful difference and is less than the PR’s ability to detect changes in accommodation.

TABLE 4.2 Results from the repeated measures two-factor analysis of variance comparing the mean accommodative lag and mean accommodative variability between age groups and by condition within each age group. RMS and LFC was log transformed due to having a non-normal distribution. The difference in means is presented prior to the p-value for accommodative lag and difference in medians is reported for RMS and LFC due to the log transformation. A positive difference for the comparison between the passive and active conditions indicates the outcome variable (accommodative lag, RMS or LFC) is highest in the passive condition. A positive difference for the comparisons of groups within the passive and active conditions indicates the outcome variable is largest in the first group listed (i.e.: group1 vs. group 2, a positive difference indicates group1 has a larger least squares mean than group 2). Significant p-values (< 0.05) are in bold.

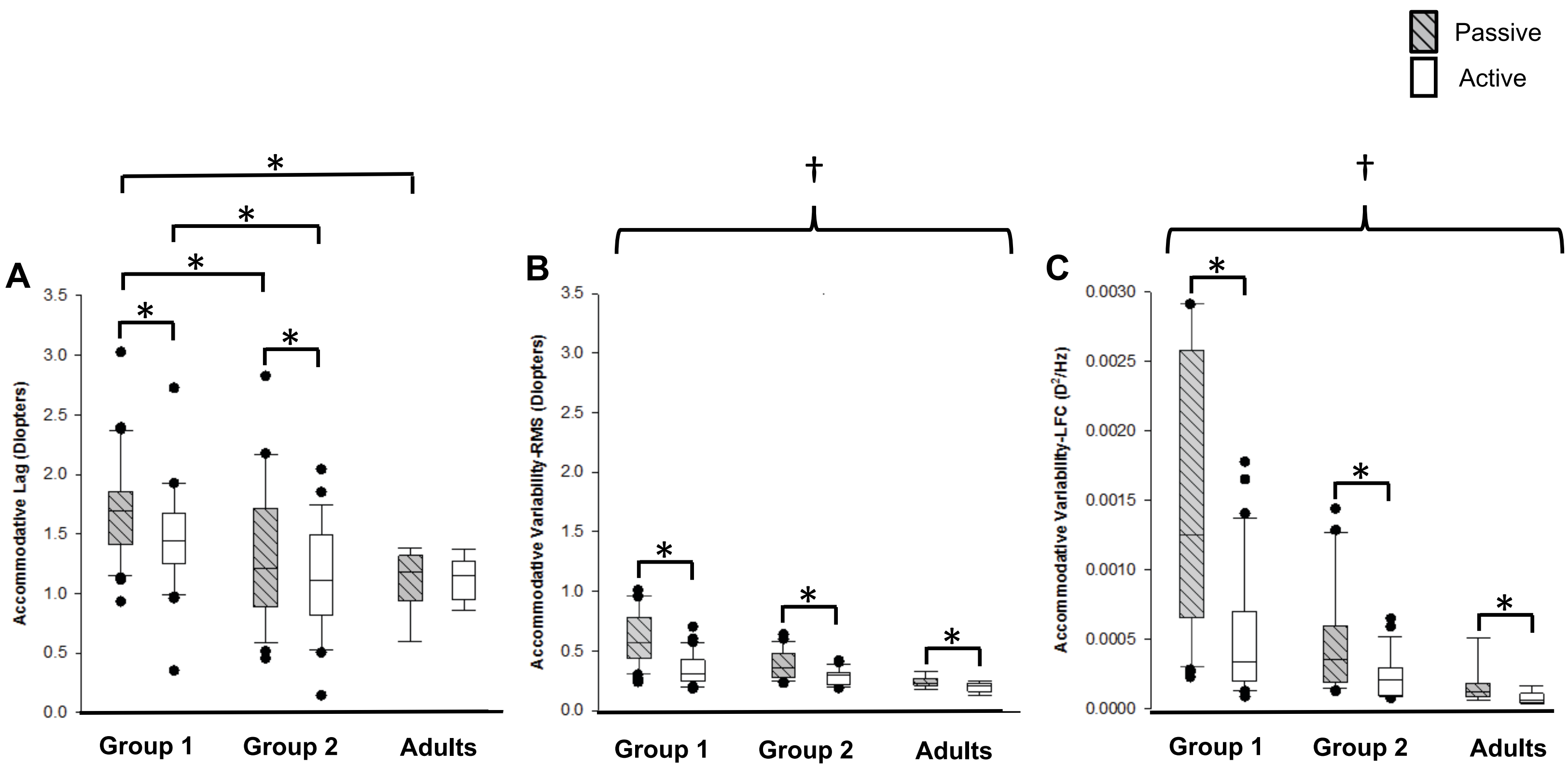
		Accommodative Lag	RMS	LFC
		Diff, p-value	**Diff, p-value**	**Diff, p-value**
Passive Vs. Active	Group 1	**0.25, <0.001**	**0.25, <0.001**	**9.10E-04, <0.001**
	Group 2	**0.21, 0.002**	**0.09, <0.001**	**1.41E-04, <0.001**
	Group 3	<0.01, 0.990	**0.04, 0.030**	**5.33E-05, 0.003**
Passive	Group 1 vs. Group 2	**0.39, 0.008**	**0.21, <0.001**	**8.94E-04, <0.001**
	Group 1 vs. Group 3	**0.60, 0.005**	**0.33, <0.001**	**1.12E-03, <0.001**
	Group 2 vs. Group 3	0.22, 0.257	**0.12, 0.027**	**2.29E-04, <0.001**
Active	Group 1 vs. Group 2	**0.33, 0.039**	0.01, 0.144	**1.25E-04, 0.009**
	Group 1 vs. Group 3	0.34, 0.137	**0.10, 0.002**	**2.66E-04, <0.001**
	Group 2 vs. Group 3	0.01, 0.970	**0.09, 0.026**	**1.41E-04, 0.003**

Next, accommodative behavior was compared across groups for each condition to determine if there was an age effect in the accuracy or stability of the accommodative response that was task dependent. In comparing accommodative lag across groups for the passive condition, Group 1 had significantly larger lags than Group 2 ($p = 0.008$) and the adults ($p = 0.005$) whereas there was no difference in lag between Group 2 and the adults ($p = 0.257$). In the active condition, Group 1 had a significantly larger lag than Group 2 ($p = 0.039$). A statistical difference was not detected for the active condition between the adults and Group 1 ($p = 0.137$) or Group 2 ($p = 0.970$) for accommodative lag.

In regards to the variability of the accommodative response, RMS was significantly higher in the passive condition than the active condition for all three groups. When comparing across groups for the passive condition, all groups were significantly different from one another with Group 1 having the greatest variability and the adults having the least (all comparisons had significance values of $p < 0.001$ with the exception of the RMS comparison between Group 2 and Group 3: $p = 0.004$). In the active condition, Groups 1 & 2 had significantly larger accommodative variability than the adults for RMS but a significant difference was not detected between Groups 1 and 2 ($p = 0.144$) for RMS.

The area under the curve for the LFC was significantly larger in the passive condition than the active condition in all three groups (Group 1: $p < 0.001$, Group 2: $p < 0.001$, Group 3: $p = 0.003$). When comparing across groups, for each condition all groups were significantly different from one another with Group 1 being most variable and the adults being the least in the passive condition ($p < 0.001$ for all comparison) and in the active condition (Group 1 vs. Group 2: $p = 0.009$; Group 1 vs. Group 3: $p < 0.001$; Group 2 vs. Group 3: $p = 0.003$).

FIGURE 4.3 Box-plot diagram showing the average accommodative lag (a), RMS (b, data is presented in its natural state rather than transformed into natural log), and LFC (c, data is presented in its natural state rather than transformed into natural log) for each of the subjects groups. Group 1 represents children who viewed shape stimuli (n = 31), Group 2 represents children who looked at text (n = 23). The adults included 8 subjects. Asterisks represent significance of $p < 0.05$. The symbol † is used to indicate significance between all group comparisons for both the passive and active viewing tasks. (Note: The data have been corrected for the interaction between eye position and refractive error measures obtained by the PR.)

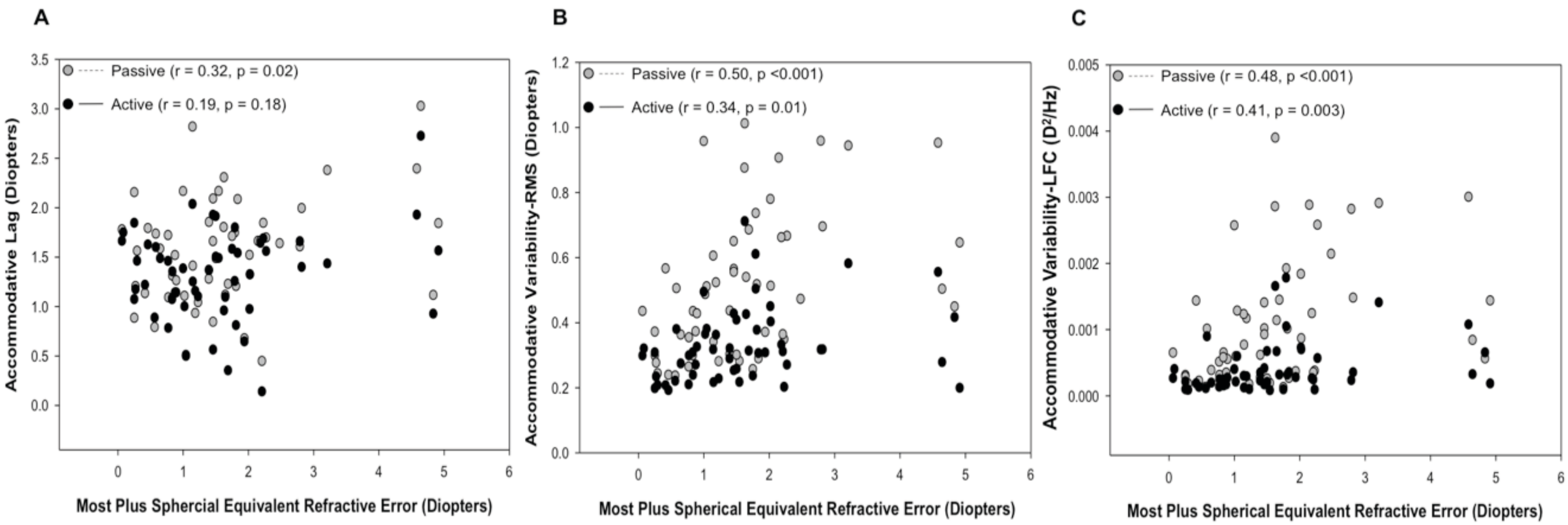


Passive
Active
A
B
C
Accommodative Lag (Diopters)
Accommodative Variability-RMS (Diopters)
Accommodative Variability-LFC (D²/Hz)
Group 1
Group 2
Adults

4.3.3 Relationships between SE and Total Accommodative Response with the Outcomes Average Accommodative Lag, RMS and LFC in Children

Given that children with greater amounts of hyperopia have greater accommodative demands than the children with lesser amounts of hyperopia, accommodative behavior was investigated as a function of refractive error for each viewing condition. Pearson's correlation was performed to investigate the relationship between accommodative lag and SE (Figure 4.4a). In the passive condition, accommodative lag was significantly associated with SE ($r = 0.32$, $p = 0.02$). However, in the active viewing condition, accommodative lag was not associated with SE ($r = 0.19$, $p = 0.18$). Spearman Rank correlation was performed to investigate the relationship between accommodative variability (RMS and LFC) and SE (Figure 4.3b and 4.3c). Both RMS and LFC were significantly associated with SE in both the passive (RMS: $r = 0.50$, $p < 0.001$; LFC: $r = 0.48$, $p < 0.001$) and active viewing conditions (RMS: $r = 0.34$, $p = 0.01$; LFC: 0.41, $p = 0.003$).

FIGURE 4.4 Scatter plots and correlations of accommodative lag (A), RMS (B), and LFC (C) with spherical equivalent refractive error in both the passive (gray circles) and active (black circles) viewing conditions for the children. Pearson's correlation coefficients are reported for accommodative lag and Spearman Rank correlation coefficients are reported for RMS and LFC due to non-normal distributions.



Given that the correlation data above includes children who viewed both shapes and letter/text stimuli, the relationship between the subjects' accommodative behavior (accuracy and variability) and SE was further explored using multivariable regression while adjusting for the stimuli viewed. The results are found in Table 4.3. In the passive viewing condition, increased SE was significantly associated with increased accommodative lag ($p = 0.042$), RMS ($p = 0.002$), and LFC ($p = 0.007$). In the active viewing condition, a significant association was not detected between SE and accommodative lag ($p = 0.292$) or RMS ($p = 0.068$), although, the relationship between SE and RMS was approaching significance. There was however a significant relationship between SE and LFC ($p = 0.043$) in the active condition. It should be noted, that the stimulus type was also found to be significant ($p < 0.05$) in both the passive and active condition for each outcome variable lag, RMS and LFC, as the subjects who viewed the letter stimuli had smaller measured values, with the exception of the active viewing condition.

TABLE 4.3 Multivariable regression models for accommodative lag, RMS and LFC with independent variable SE while adjusting for stimulus type (shapes or letters/text) for all children. Beta-coefficients, 95% confidence intervals (CI) and p-values are reported for each viewing condition. Significant p-values are reported in bold.

		Passive (*n* = 54)			Active (*n* = 53)		
		Beta-coeff	**95% CI**	**p-value**	**Beta-coeff**	**95% CI**	**p-value**
Accommodative Lag	**Intercept**	1.83	1.35 to 2.32	**<0.001**	1.71	1.30 to 2.13	**<0.001**
	SE	0.13	0.005 to 0.25	**0.042**	0.05	-0.05 to 0.16	0.292
	Stimuli	-0.34	-0.61 to -0.06	**0.018**	-0.33	-0.57 to -0.09	**0.008**
RMS	**Intercept**	0.68	0.50 to 0.85	**<0.001**	0.37	0.27 to 0.48	**<0.001**
	SE	0.07	0.03 to 0.11	**0.002**	0.02	-0.001 to 0.05	0.063
	Stimuli	-0.19	-0.29 to -0.09	**<0.001**	-0.06	-0.12 to 0.003	0.063
LFC	**Intercept**	1.90E-3	1.2E-3 to 2.7E-3	**<0.001**	6.40E-4	3.0E-4 to 9.8E-4	**<0.001**
	SE	2.50E-4	7.3E-5 to 4.4E-4	**0.007**	8.70E-5	2.8E-6 to 1.7E-4	**0.043**
	Stimuli	-9.00E-4	-1.3E-3 to -4.8E-5	**<0.001**	-2.6E-4	-4.5E-4 to -6.3E-5	**0.011**

If all children accommodated to have equivalent accommodative lags, the results of the regression analysis above would be similar whether using spherical equivalent or the total accommodative response as the outcome variable. However, not all subjects are likely to have equivalent accommodative lags and thus the linear regression models regarding stability of the response were repeated to investigate the relationship between the total accommodative response and accommodative variability. A significant association was detected between increased total accommodative response and RMS in both the passive and active viewing conditions (passive: $p = 0.014$; active: $p = 0.003$) and between the total accommodative response and LFC in the active condition ($p = 0.008$). A significant relationship was not detected between the total accommodative response and LFC in the passive viewing condition ($p = 0.058$).

TABLE 4.4 Multivariable regression models for RMS and LFC with independent variable total accommodative response (calculated in the vertical meridian) while adjusting for stimulus type (shapes or letters/text) for all children. Beta-coefficients, 95% confidence intervals (CI) and p-values are reported for each viewing condition. Significant p-values are reported in bold.

		Passive (*n* = 54)				Active (*n* = 53)		
		Beta-coeff	**95% CI**	**p-value**		**Beta-coeff**	**95% CI**	**p-value**
RMS	**Intercept**	0.65	0.44 to 0.86	**<0.001**		0.30	0.18 to 0.42	**<0.001**
	Total Accommodative Response	0.06	0.01 to 0.11	**0.014**		0.04	0.01 to 0.06	**0.003**
	Stimuli	-0.22	-0.32 to -0.12	**<0.001**		-0.07	-0.12 to -0.008	**0.026**
LFC	**Intercept**	1.90E-3	1.0E-3 to 2.8E-3	**<0.001**		4.5E-4	6.1E-5 to 8.4E-4	**0.024**
	Total Accommodative Response	1.9E-4	-6.56E-6 to 3.9E-4	0.058		1.2E-4	3.2E-5 to 2.0E-4	**0.008**
	Stimuli	-1.0E-3	-1.4E-5 to -5.7E-4	**<0.001**		-2.9E-4	-4.8E-4 to -9.8E-5	**0.004**

4.3.4 Interaction between SE and Time on the Outcomes Accommodative Lag, RMS and LFC

Next, because each viewing condition lasted 10 minutes each, it is feasible that the accommodative behavior (accuracy and variability) may change over time. Given that children with greater amounts of hyperopia have greater demands, it is feasible they may be more susceptible to fatigue throughout the experiment and thus may experience a decrease in the accommodative response (i.e.: greater accommodative lag) or even a more variable accommodative response if they begin to experience drifts in accommodation. Thus, random effects linear models were used to determine if changes in the accommodative response or accommodative variability over time in either viewing condition were significantly associated with levels of uncorrected hyperopia in either experimental group or the adult control group. The results are found in Table 4.5. The random effects models detected a significant effect ($p < 0.05$) of the interaction between time and the magnitude of uncorrected hyperopia on accommodative lag in the passive condition for both experimental groups and the control group, as well as the active condition for Group 2. The random effects models detected a significant effect ($p < 0.05$) of the interaction between time and the magnitude of uncorrected hyperopia on RMS in Group 1 in the passive condition. The random effects models did not detect a significant effect ($p > 0.05$) of the interaction between time and the magnitude of uncorrected hyperopia on the LFC for any group or condition.

The original analysis did not require a minimum number of data points per bin for analysis. Thus, to ensure that bins with missing data did not impact the results, the data were re-analyzed while excluding bins that were missing ≥ 60% of possible data points (missing ≥ 150 data points of possible 250). Despite small changes in the beta-coefficients the general trends and significance remained unchanged for all models.

TABLE 4.5 Random effects mixed linear model of accommodative lag and variability in the time domain (RMS) and frequency domain (LFC) as a function of uncorrected spherical equivalent hyperopic refractive error, time and the interaction between time and uncorrected refractive error.

			Accommodative Lag		RMS		LFC	
Age Category	Condition	Predictor	β Coefficient	p-value	β Coefficient	p-value	β Coefficient	p-value
Group 1	Passive *n* = 31	Time	-0.003	0.703	-0.005	0.205	-5.85E-04	0.355
		SE	0.196	0.001	0.051	0.039	2.27E-03	0.148
		Time*SE	0.009	**0.01**	0.002	0.321	1.94E-04	0.485
		Intercept	1.098	-	0.348	-	9.77E-03	-
	Active *n* = 30	Time	-0.012	<0.001	0.002	0.305	8.39E-06	0.55
		SE	0.121	0.03	0.021	0.201	5.41E-04	0.559
		Time*SE	0.003	0.115	0.002	0.124	8.48E-05	0.093
		Intercept	1.114	-	0.235	-	3.04E-03	-
Group 2	Passive *n* = 23	Time	-0.014	<0.001	-0.001	0.487	-3.60E-04	0.801
		SE	-0.035	0.744	0.022	0.132	-3.96E-04	0.268
		Time*SE	0.01	**<0.001**	0.002	**0.013**	2.92E-04	0.203
		Intercept	1.192	-	0.274	-	4.72E-03	-
	Active *n* = 23	Time	-0.021	<0.001	0.001	0.583	-8.90E-05	0.654
		SE	-0.054	0.507	0.004	0.688	1.56E-04	0.469
		Time*SE	0.005	**<0.001**	0.001	0.091	7.72E-05	0.333
		Intercept	1.076	-	0.234	-	1.73E-03	-
Group 3	Passive *n* = 8	Time	0.013	0.002	-0.001	0.709	2.75E-06	0.801
		SE	-0.278	0.225	0.008	0.789	1.03E-04	0.268
		Time*SE	-0.010	**0.02**	0.002	0.41	4.79E-05	0.203
		Intercept	1.145	-	0.213	-	1.31E-03	-
	Active *n* = 8	Time	0.002	0.67	0.000	0.777	-1.78E-05	0.654
		SE	-0.080	0.624	-0.003	0.933	1.29E-04	0.469
		Time*SE	-0.005	0.182	0.000	0.764	2.01E-05	0.333
		Intercept	1.003	-	0.179	-	7.30E-04	-

4.4 Discussion

The purpose of this study was to investigate accommodative lag and accommodative variability in young hyperopes between the ages of 3 and < 10 years over a longer duration of time and during tasks varying in cognitive demands. The results of this study demonstrate the influence of cognition on the accuracy and variability of the accommodative response in children, as the accommodative accuracy and stability improved under active viewing conditions (Figures 4.3 & 4.4). This study also demonstrates that under sustained near viewing conditions in children aged 3 to < 10 years, uncorrected hyperopia is associated with increased accommodative lag and increased RMS during the passive viewing tasks used in this study, independent of which stimuli the subjects viewed (shapes vs. letters/text). However, under sustained viewing conditions in which the subjects are more actively engaged, the significant interactions between increased accommodative lag and increased RMS were no longer detected.

Our results are in agreement with other studies that have shown that accommodative lag decreases during near viewing tasks that require more cognitive effort (Kruger 1980, Woodhouse, Cregg et al. 2000, Francis, Jiang et al. 2003). However, we found that to be true only for the children, as a significant difference of accommodative lag was not detected between the passive and active viewing conditions in the adult subjects (Table 4.2, Figure 4.3). Bullimore & Gillmartin (1988) also did not find a find a difference in accommodative lag between a passive and active viewing task in adults at 33 cm (Bullimore and Gilmartin 1988). Thus, the accommodative system of adults may not be as susceptible to cognitive effort as children.

In addition to the effect of cognition on accommodative lag, the results of this study suggest that increased cognitive effort is also associated with a significant decrease in accommodative variability resulting in a more stable accommodative response in both the children and the adults, despite the overall increase in the mean accommodative response seen in the children (Table 4.2). Our data also suggest that on average, the stability of the accommodative response improves with age as the youngest children in Group 1 had the most variable responses while the adults had the least variable. It is worth noting however that Groups 1 and 2 overlapped at age 6 (some 6 year olds viewed the shapes while others viewed the letters/text) due to different cognitive abilities and thus there is ambiguity in the results regarding how much of the differences detected between the groups is due to age versus being due to differences in the stimuli. The effect of cognitive effort on accommodative variability has not been previously investigated, and thus there are no other studies for which to compare our results.

A decrease in accommodative variability with an increase in accommodative response is contrary to what one may expect based on previous studies that have found accommodative variability increases with an increase in the accommodative response (Kotulak and Schor 1986, Candy and Bharadwaj 2007, Anderson, Glasser et al. 2010). However, the results of this chapter are in agreement with the results in Chapter 2 as both chapters have demonstrated that, on average, as the accommodative response became more accurate, the accommodative response was also more stable. It is feasible, however, that there was not a sufficiently large enough increase in the accommodative response to result in an increase in accommodative variability given that Kotulak and Schor (1986a) found that RMS increased 0.05 D/1 D of accommodative response in adults (Kotulak and Schor 1986) and on average the difference in the accommodative responses between the active and passive conditions were 0.26 D for the youngest children and 0.21 D for the older children (Table 4.2). Additionally, when considering the increase in RMS/D of accommodation presented by Kotulak and Schor, we also had similar beta-coefficients in our model when the total accommodative response was the independent variable (Table 4.4)

The results of this study are also in agreement with other studies that have shown that children with increased levels of uncorrected hyperopia tend to have increased levels of accommodative lag (Mutti 2007, Horwood and Riddell 2011, Candy, Gray et al. 2012, Tarczy-Hornoch 2012) (Figure 4.3a). However, the increase in accommodative lag as a function of SE was detected only in the passive condition (Figure 4.3, Table 4.3). This suggests that children with increased amounts of hyperopia are able to accommodate a sufficient amount to have a similar accommodative lag to children with lesser amounts of hyperopia, but that perhaps the magnitude of their accommodative response is more influenced by their cognitive demand.

Accommodative variability (RMS and LFC) was also evaluated as a function of SE in both the passive and active viewing conditions in the children. In the time domain, increased uncorrected hyperopia was independently associated with RMS in the passive viewing condition, but not in the active viewing condition, although it was approaching significance (Table 4.3). These results suggest that when performing a visual task passively, children with greater amounts of hyperopia have an overall more variable accommodative response than those with lesser amounts of hyperopia but when cognitively engaged in the task, the accommodative stability of children with larger amounts of uncorrected hyperopia was similar to children with lesser amounts of hyperopia despite their increased accommodative demand. The results may be surprising given that the children with greater amounts of hyperopia had similar accommodative lags than children with lesser amounts of hyperopia and thus had to maintain a higher level of accommodative response throughout the task, and yet there was not a difference in RMS as a function of SE. The absence of an expected independent significant relationship between RMS and SE may be accounted for in the frequency domain, as an increase in LFC was significantly associated with increased SE in both the passive ($p = 0.007$) and active ($p = 0.043$) viewing conditions. The results of the LFC regression analysis would suggest that, as expected, the children with greater amounts of hyperopia did have larger drifts of their accommodative response in both viewing conditions as compared to children with lesser amounts of hyperopia. While there was a difference in the impact of SE on accommodative variability in time and frequency domains in the active viewing condition, the trends were similar in that both respective beta-coefficients were smaller in the active condition in comparison to the passive condition, despite the differences in significance for SE in the respective models (Table 4.3). When considering the relationship between SE and accommodative variability along with accommodative accuracy, SE was significantly associated with both increased lag and increased RMS in the passive condition but was not significant for either outcome variable in the active condition. These results are also in agreement with our observation that as accommodation becomes more accurate (i.e.: lag decreases), the response becomes more stable.

While there are trends in the data suggesting that children with uncorrected hyperopia may have increased accommodative lags or variability, the data is quite variable as shown in Figure 4.4. For example, the inspection of Figure 4.4 shows that one child with ~5 D of hyperopia has approximately a 2 D lag of accommodation during the active viewing task. However, there are also children with much lesser amounts of hyperopia with nearly equivalent accommodative lags. Examples such as these are found throughout Figures 4.4. One child that is particularly interesting had +4.91 D SE of uncorrected hyperopia yet also had one of the most stable mean responses of all subjects (RMS = 0.20 D), including the adults. Thus, while the data suggest that children with increased amounts of uncorrected hyperopia may have a larger accommodative lag or more variable accommodative response, especially in the passive viewing condition, it is not the case for all children.

In addition to the magnitude of uncorrected hyperopia, the magnitude of the accommodative response should also be considered when studying accommodative variability in hyperopic children. It would be expected that SE and accommodative response would be highly correlated if all subjects had similar accommodative lags. However, as seen in Figure 4.4, not all children had similar accommodative lags. As noted above, SE was independently associated with lag, RMS and LFC in the passive condition but only significantly associated with LFC in the active condition. It is important to consider that the multivariable regression did not account for the amount of accommodation actually exerted by all subjects. If the total accommodative response is considered, there is a significant association between total accommodative response and accommodative variability (RMS for both viewing conditions and for LFC in the active task and approaching significance in the passive task) (Table 4.4). However, we did not see the same relationship between the total accommodative response and RMS in Chapter 2 as we did in this chapter. In the current Chapter, there was a significant relationship between the total accommodative response and RMS in both the passive and active viewing conditions. In Chapter 2, there was not a significant relationship between the total accommodative response and RMS (Figure 2.4 in the blur+disparity condition at 33 cm). This suggests that RMS is not influenced solely by the accommodative response or even the accommodative lag, as discussed above, but rather is likely a combination of the two factors and possibly other factors not considered in this work, such as an individual's aberrations.

This was the first study to measure the change in accommodative lag over an extended period of time (> 30 seconds) in children with uncorrected hyperopia. The results indicate that as time progressed throughout the experiments, the children with greater amounts of hyperopia who viewed the shape stimuli (Group 1) experienced an increase in accommodative lag throughout the duration of the experiment. Using the beta coefficients from Table 4.5, a child with +1.00 D of uncorrected hyperopia would be estimated to have a 1.30 D lag at the beginning of viewing a passive task which would be estimated to increase to 1.35 D over a 9 minute period, whereas a child with +3.50 D of uncorrected hyperopia would begin with a larger lag of +1.80 D, which would increase to an estimated +2.00 D over the course of 9 minutes on average. While the increase in accommodative lag is only 0.20 D over the course of the 10 minutes, the difference in accommodative lag between the two children (+1.00 D and +3.50 D child) is estimated to be ~0.70 D by the end of the 10 minutes and would be expected to be greater for children with uncorrected hyperopia greater than +3.50 D SE. It is unknown if the disparity in the magnitude of accommodative lag would increase even further if the experiment had a longer duration. Conversely, when actively viewing a task, the changes over time were no longer apparent in Group 1. While there was not an increase in lag over time detected within the 10 minutes of testing in the active task, it should be noted that the child with +3.50 D of uncorrected hyperopia would have an estimated 0.40 D greater accommodative lag on average than the +1.00 D child.

The model for the older children predicted that a child with +3.50 D uncorrected hyperopia would have a similar accommodative lag to a child with +1.00 D of uncorrected hyperopia (1.09 D vs. 1.15 D) at the beginning of a passive task that would then increase over time by 0.15 D whereas the +1.00 D child would remain steady over time. While the model indicates that a change of 0.15 D is significant, it may not be clinically meaningful. However, children with greater than +3.50 D of uncorrected hyperopia would be predicted to have even larger changes over time, which may become clinically meaningful depending upon the magnitude of the uncorrected hyperopia. As with the passive task, the model for the active task predicts the +3.50 D hyperope would have a slightly smaller accommodative lag than the +1.00 D hyperope (0.88 D vs. 1.00 D) at the beginning of the task, but the average lag would not change over time. A +1.00 D hyperope on the other hand would be predicted to improve their accommodative accuracy as the duration of the task increased to the 9-minute point where both the +1.00 and +3.50 D child would be predicted to have similar accommodative lags (0.85 D vs. 0.87 D). Thus, the random effects linear models suggest that uncorrected hyperopia results in significantly larger accommodative lags over time in both Groups 1 and 2 in the passive viewing tasks but the magnitude of the changes over time are quite small (< 0.25 D) and may not be clinically meaningful.

Increased variability over time related to uncorrected hyperopia was only found in the older children in the passive task. Using the beta coefficients from Table 4.5 for change in RMS over time, it would be predicted that a child in Group 2 with +3.50 D of hyperopia would have 0.10 D greater RMS at 9 minutes as compared to a child who had only +1.00 D of uncorrected hyperopia. An increase in RMS was not found over time in Group 1 during the passive (or active) task despite having a larger increase in accommodative lag throughout the task (predicted ~0.25 D for a +3.50 D hyperope). The lack of a significantly detectable change in variability of the response over time may be due to the large range of accommodative variability in Group 1 as represented by the median and interquartile range in Table 4.1. The larger range of variability of the response may make it more difficult in detecting a statistically significant change over time.

The results of this chapter follow the same general trend as those found in Chapter 2, in that when the accommodative demand is kept constant (similar stimuli at same viewing distance), if the mean accommodative response increases, the response also became more stable. In the current chapter, the response increased and was more stable in the active task as compared to the passive task, while in Chapter 2, the response increased and was more stable in the blur+disparity condition as compared to the blur-only conditions. This chapter is also similar to Chapter 2 in that the children generally have less accurate and less stable responses than adults. This chapter also revealed inconsistencies in the relationships between accommodative accuracy and variability with independent variables such as SE and the total accommodative response. For example, in Chapter 2 a significant relationship between the total accommodative response and RMS was not detected, whereas they were significantly associated in this chapter under both the passive and active viewing conditions. The differences in the relationships could be due to differences in duration of the tasks. However, there were inconsistencies in relationships even within this chapter given the differences in significance of SE in relation to accommodative lag and RMS between the two viewing conditions. Thus, an important finding of this chapter is that accommodative behavior is quite variable, especially in terms of the relationship between SE, accommodative lag and accommodative stability.

4.4.1 Study Limitations

A possible limitation of the study is that the pupil was allowed to vary throughout the experiments and pupil size is known to affect the variability of accommodation (Gray, Winn et al. 1993). While the data were excluded if the pupil size was <4 mm, we evaluated the correlation between pupil size and refractive error measures obtained by the PR (after data points had been removed if they met the exclusion criteria described in section 4.2.5). The correlations in the passive viewing condition had a range of -0.29 to 0.49 with a mean ± *sd* correlation value of 0.08 ± 0.18 while the active condition had a range of -0.21 to 0.52 with a mean correlation value of 0.09 ± 0.17. Of the 54 children and 8 adults who participated, only 8 children and 1 adult had correlations ≥ 0.30 in the passive viewing condition (correlations < 0.30 are considered to be weak correlations), suggesting changes in pupil size did not systematically alter our results.

There are possible limitations to the study. First, children involved in the study were as young as 3 years of age and there may be concern that the youngest subjects did not cooperate throughout the duration of the study given the length of both experimental conditions. However, studies of sustained visual attention and distractibility suggest that on average, children greater than 3 years of age are capable of sustaining a visual task for 10 minutes of time (Ruff, Capozzoli et al. 1998) and are less distractible while performing a task requiring attention (Ruff and Capozzoli 2003). Distractions during the study were limited by dimming the lights during testing and placing a curtain above and on either side of the stimulus apparatus to limit the field of view to the stimulus only. Only one child recruited between the ages 3 to < 6 years was unable to complete either experimental condition, and 88% of participants completed the passive viewing condition and 84% of participants completed the active viewing condition and 100% of subjects ≥ 6 years completed both experiments. Thus cooperation was not problematic for the vast majority of the young children. An additional concern is that the subjects may fatigue during the first condition and the subsequent condition would reveal worse accommodative behavior. However, the order of the conditions was counter-balanced across subjects in an attempt to eliminate any affect the order of testing may have had on the results.

An additional concern with the study is that the cognitive demand was assumed to be different between the passive and active tasks. It is possible however that some subjects were not cognitively challenged in the active task or were more challenged in the passive task. For example, the adult subjects who did not exhibit the expected decrease in accommodative lag during the active condition may have found it challenging to view as many letters as possible during the passive task, or they could have found the

Master's Thesis in Economics less cognitively stimulating than the investigators had anticipated. Future studies of cognitive effort on accommodative behavior should be sure that there is clear differentiation between the cognitive requirements in the passive and active viewing tasks to better control for the effect that cognition has on accommodation. The neuroscience approach to studies on cognitive effort suggests that tasks that involve decision-making paradigms are more demanding of cognition (Westbrook and Braver 2015). Thus future studies should consider using two stimuli where one requires the subject to only view the stimulus while the other requires the subjects to make decisions about what they see. This approach was done with the subjects who viewed the shapes, but was not necessarily done for the subjects who read passages.

4.4.2 Summary

In summary, the results from this study suggest that on average, increased cognitive effort improves accommodative accuracy and accommodative stability in children aged 3 to < 10 years of age. The results from this study also demonstrate that while children with higher amounts of hyperopia experience increased levels of accommodative lag and accommodative variability when performing a sustained accommodative task, the significant association between accommodative lag and variability is inconsistent given that increased accommodative lag and accommodative variability were significantly associated with SE when passively viewing the stimuli but a significant association was not detected with actively viewing the stimuli. It was also demonstrated that accommodative lag tends to increase over time in younger children with increased levels of uncorrected hyperopia under a passive viewing condition, however, that small of change over a 10-minute period (~0.25 D predicted change for a +3.50 D hyperope) may not be clinically meaningful. Lastly, as with previous chapters, the results suggest that children < 10 years of age tend not to have adult-like accommodative behavior (accommodative accuracy and stability) under passive or active viewing conditions.

CHAPTER 5: Cumulative Discussion and Summary of the Body of Work Presented in Previous Chapters

The purpose of this dissertation was to investigate the differences in accommodative behavior both in terms of accuracy and variability in children in a number of experimental conditions while attempting to gain insight into how accommodative behaviors are influenced by the magnitude of uncorrected hyperopia. The experiments in Chapter 2 of the dissertation were conducted to gain an understanding of the impact that blur and disparity cues have on both the mean accommodative response and accommodative variability. The experiment in Chapter 3 of this dissertation was designed to understand the relationship between accommodative microfluctuations and blur detection thresholds. If accommodative microfluctuations acted as sub-threshold blur detectors in children then it would be expected that the magnitude of accommodative microfluctuations and blur detection thresholds would be correlated. Additionally, blur detection thresholds are considered to be a similar measure of DOF and thus Chapter 3 also investigated DOF and accommodative microfluctuations. Prior to this dissertation, DOF had not yet been studied in children. Previous authors have shown that the level of cognitive effort exerted during a task influences the magnitude of the accommodative response. This has been shown in both children (Woodhouse, Cregg et al. 2000) and adults, although the results in adults have been inconsistent (Kruger 1980, Bullimore and Gilmartin 1988, Woodhouse, Cregg et al. 2000). The impact cognitive effort has on accommodative variability has not yet been studied. Thus, the experiments in Chapter 4 were designed to investigate the impact of cognitive effort not only accommodative accuracy, but also on accommodative variability. Lastly, accommodative behavior in terms of accuracy and variability has not been measured in children beyond a 30 second period. Thus, Chapter 4 was also designed to investigate the accuracy and variability of the accommodative response over time during the passive and active viewing conditions.

5.1 Impact of Blur and Disparity Cues on Accommodative Accuracy and Accommodative Variability

The results of Chapter 2 revealed that in children, the accommodative response was greatest and most stable when blur and disparity cues were available (Figure 2.2). The accommodative response decreased and became variable when disparity cues were removed from the stimulus under monocular viewing conditions. A similar trend was not found in the adult subjects as a significant difference in the accommodative response or RMS was not detected between the blur+disparity and blur-only conditions. As expected, in both children and adults the accommodative response was least when blur cues were removed from the stimulus such that accommodation was open loop. Despite the decreased accommodative response in the disparity-only condition as compared to the blur+disparity condition for both children and adults, a coinciding significant increase in accommodative variability was only detected in the children. The results are in agreement with other studies that suggest that blur cues are more important than disparity cues in regards to the magnitude of the accommodative response (Heath 1956, Mays and Gamlin 1995, Bharadwaj and Candy 2008). The results also suggest that in the presence of blur cues, disparity cues help to facilitate a more accurate and more stable accommodative response in children, whereas the availability of disparity cues in the presence of blur cues do not appear to be as important in the mature adult visual system.

In addition to investigating the impact that the removal of blur and disparity cues have on the accommodative response, the experiments in Chapter 2 also investigated the impact of blur and disparity cues when they were uncoupled in visual direction by the use of -2.00 D lenses or 2 MA base-out prism. While the total accommodative response was significantly largest in the prism-induced condition and significantly smallest in the blur-induced condition, a difference in RMS was not detected across conditions. These results are somewhat perplexing because a difference in RMS across the conditions would have been expected given the differences in the total accommodative response and thus differences in lag across the conditions.

5.2 Accommodative Variability as a Function of the Magnitude of the Total Accommodative Response

Previous authors have shown that as the accommodative response increases, RMS increases as well (Kotulak and Schor 1986, Candy and Bharadwaj 2007, Anderson, Glasser et al. 2010). The previous studies were conducted with a repeated measures testing paradigm where individual subjects viewed a stimulus that increased in accommodative demand throughout testing, thus eliciting an increased accommodative response. Our hypothesis that an increase in the total accommodative response would result in an increase in accommodative variability was evaluated by characterizing the relationship between the total accommodative response and RMS using two different methods. In the first method, we calculated the change in the total accommodative response between the 100 cm and 33 cm viewing distances, a similar method to those used in studies mentioned above. The analysis consisted of within subject comparisons for each condition tested (blur+disparity, blur-only and disparity-only) using repeated measures t-test. Similar to previous studies with similar methodology, we found an increase in total accommodative response as well as an increased in accommodative variability (RMS) in each of the comparisons (data summarized in Table 5.1) when comparing the accommodative behavior at 100 cm to 33 cm.

TABLE 5.1 Summary data from Chapter 2 of the change in the total accommodative response and change in RMS from the blur+disparity, blur-only and disparity-only conditions. The difference in mean values from the 100 cm and 33 cm viewing distances for the outcome variables total accommodative response and RMS are presented prior to the p-value for each viewing condition. The positive difference for both accommodative response and RMS indicate larger values at the 33 cm testing distance.

		Total Accommodative Response	RMS
		Diff, p-value	**Diff, p-value**
Blur+disparity	All Children	1.43, <0.001	0.20, <0.001
	Adults	1.47, <0.001	0.07, <0.001
Blur-only	All Children	1.01, <0.001	0.24, <0.001
	Adults	1.58, <0.001	0.09, <0.001
Disparity-only	All Children	0.55, <0.001	0.30, <0.001
	Adults	1.08, <0.001	0.14, 0.002

The second method we used to characterize the relationship between RMS and the accommodative response was to calculate the total accommodative response for each subject based on their cycloplegic SE refractive error in the vertical meridian of the right eye in Chapter 2 and the most plus eye in Chapter 4 when viewing the stimulus at 33 cm. The data from Chapters 2 and 4 that used this method are summarized in Table 5.2.

TABLE 5.2 Unadjusted and adjusted (age or stimuli) regression models for accommodative RMS with independent variable total accommodative response for each condition that analyzed RMS as a function of total accommodative response in chapters 2 & 4. Beta-coefficients, 95% confidence intervals (CI) and p-values are reported for each viewing condition. Significant p-values for total accommodative response are reported in bold.

		Unadjusted			Adjusted		
		Beta-coeff	95% CI	p-value	Beta-coeff	95% CI	p-value
Blur + Disparity	**Intercept**	0.34	0.18 to 0.50	<0.001	0.6	0.30 to 0.55	<0.001
	Total Accommodative Response	0.02	-0.03 to 0.08	0.457	0.01	-0.04 to 0.07	0.701
	Age	-	-	-	-0.03	-0.7 to -0.0003	0.048
Blur-Only	**Intercept**	0.44	0.30 to 0.57	<0.001	0.66	0.41 to 0.91	<0.001
	Total Accommodative Response	0.01	-0.04 to 0.07	0.595	0.02	-0.3 to 0.70	0.498
	Age	-	-	-	-0.04	-0.08 to -0.002	0.037
Disparity-only	**Intercept**	0.47	0.33 to 0.61	<0.001	0.7	0.40 to 0.99	<0.001
	Total Accommodative Response	0.1	0.31 to 0.17	**0.006**	0.1	0.03 to 0.17	**0.009**
	Stimuli	-	-	-	-0.04	-0.08 to 0.005	0.081
Passive	**Intercept**	0.34	0.16 to 0.51	<0.001	0.65	0.44 to 0.86	<0.001
	Total Accommodative Response	0.06	0.005 to 0.11	**0.034**	0.06	0.01 to 0.11	**0.014**
	Stimuli	-	-	-	-0.22	-0.32 to -0.12	<0.001
Active	**Intercept**	0.21	0.12 to 0.30	<0.001	0.3	0.18 to 0.42	<0.001
	Total Accommodative Response	0.04	0.01 to 0.06	**0.005**	0.04	0.01 to 0.06	**0.003**
	Stimuli	-	-	-	-0.07	-0.12 to -0.008	0.026

Due to the varying amounts of uncorrected hyperopia, which resulted in various measures of the total accommodative response, we were able to analyze RMS as a function of total accommodative response across children using linear regression for the data collected in both Chapters 2 and 4. In Chapter 2, we did not find a relationship between RMS and the total accommodative response in the unadjusted analysis or when the analysis was adjusted for age (Figure 2.4 shows unadjusted means, Table 5.2 summary table) in either the blur+disparity or blur-only conditions. As expected, there was a significant relationship detected between RMS and the total accommodative response in the disparity-only condition. In Chapter 4, a significant relationship was found between RMS and the total accommodative response when adjusting for the stimuli viewed (shapes vs. letters/text) (Table 4.4). The question then becomes, why was there a difference in results between the two chapters, specifically when comparing the results of passive and active viewing condition to the blur+disparity condition since they were both measured under similar full-cue viewing conditions.

Taking a step back, previous studies have suggested that RMS increases with an increase in the accommodative response due to increased noise in the accommodative plant (Kotulak and Schor 1986, Gray, Winn et al. 1993). However, this theory only considers that an increase in RMS is due to an underlying motor mechanism. We must keep in mind that it has also been demonstrated that an increase in the accommodative response also results in an increase in accommodative lag (Gwiazda, Thorn et al. 1993, Abbott, Schmid et al. 1998, McClelland and Saunders 2004, Anderson, Glasser et al. 2009, Roberts, Anderson et al. 2015). In revisiting Figure 2.2 but this time viewing it in terms of change in lag as opposed to change in accommodative response by using the last column labeled “Total Accommodative Demand” (average total demand for all children, children ≤ 1.15 D, and adults based on each groups mean SE), it is clear that our subjects also exhibited an increase in accommodative lag along with an increased accommodative response for the 33 cm viewing condition as compared to the 100 cm viewing condition. Thus, there may also be an underlying sensory mechanism that is contributing to the increase in RMS. This is particularly evident when comparing the blur+disparity and blur-only conditions of Chapter 2 and the passive and active viewing conditions of Chapter 4 where all 4 experimental conditions were performed at 33 cm, thus there was no difference in accommodative demand across conditions and there was no change in the stimulus (spatial frequency, contrast, etc.). In both chapters we found that the condition that had the greatest accommodative response (blur+disparity and the active viewing condition) also had the most stable accommodative response. In other words, when the accommodative response was least accurate, the response was also more variable.

When considering the question proposed above regarding the inconsistencies in the relationship between RMS and the total accommodative response in the blur+disparity condition and the two sustained conditions (passive and active viewing conditions), the answer may lie in the relationship between the magnitude of the total accommodative response and the accommodative lag of each subject. For example, if a child with +1.00 D SE accommodated 3 D for a stimulus located at 33 cm, they would have a +1.00 D lag. If a child with +4.00 D SE also accommodated 3 D for a stimulus located at 33 cm, they would have a lag of accommodation of 4 D. Thus, it is likely that RMS cannot be predicted by either a motor or sensory mechanism in isolation, but rather that RMS may be influenced by a combination of the two mechanisms. Variability in individuals' total accommodative response across conditions would also alter their lag of accommodation, which could impact their RMS values. The linear regressions performed in Chapters 2 (Figure 2.4) and 4 (Table 4.4) regarding RMS as a function of the total accommodative response did not account for the magnitude of the accommodative lag for each subject during the experiment, which may account for differences in the relationships between RMS and the total accommodative response across experiments. Thus it appears that the magnitude of RMS cannot be predicted solely by the total accommodative response or by accommodative lag. More studies need to be performed in this area to further understand these relationships as well as to investigate any other potential variables that may contribute to the accuracy and stability of the accommodative response.

5.3 Associations between RMS, Blur Detection Thresholds and DOF

Accommodative microfluctuations are thought to act as sub-threshold blur detectors in the adult visual system where accommodative variability, when represented as RMS, is smaller than the DOF of the eye (Kotulak and Schor 1986, Yao, Lin et al. 2010). It has also been shown that as the DOF increases, RMS increases as well (Gray, Winn et al. 1993, Yao, Lin et al. 2010). Subjective blur detection may be measured using a variety of methods, two of which were used in Chapter 3. The first method is to add blur to the stimulus, as was done in the blur detection task, and then determine the minimum amount of blur that could be detected between the clear and blurred stimulus for each subject. The second method used is by measuring the subjective DOF of the subjects by having them fixate the stimulus and identify the distal and proximal edges of the DOF. The work in this dissertation is the first to study blur detection and DOF in children under the age of 10 years.

We hypothesized that if accommodative microfluctuations act as sub-threshold blur detectors as suggested by Kotulak and Schor (1986b) and Yao et al (2010) then an increase in RMS would be significantly associated with increased blur detection thresholds (Kotulak and Schor 1986, Yao, Lin et al. 2010). The results of Chapter 3 support this hypothesis, as RMS was found to be independently associated with increased blur detection thresholds when controlling for other potential confounding variables such as uncorrected hyperopic refractive error, age and accommodative lag (Table 3.2).

In addition to measuring blur detection thresholds, DOF measures were also attempted on children older than 6 years of age. The DOF experiment was difficult for the children to perform as only ~2/3 of the children were able to complete the task. Despite only a limited number of children being able to complete the task, the results are in agreement with Kotulak & Schor (1986b) and Yao et al (2010) in that the RMS values measured in the blur detection task were less than the obtained measures of DOF even when doubling the RMS to account for the predominant range over which accommodation fluctuated (Kotulak and Schor 1986, Yao, Lin et al. 2010).

The results of Chapter 3 also suggests that children less than 10 years of age, on average, do not have adult-like abilities to process blur as they had larger blur detection thresholds and increased levels of DOF than the adult subjects. The comparisons of the blur detection thresholds were done not only by comparing all children to the adults, but also by comparing only children with similar upper limit of refractive error as the adult subjects in an attempt to rule-out refractive error as a confounding variable for the comparison. Even with similar upper limit refractive error distributions (+1.51 SE) the children still had significantly higher blur detection thresholds than the adults. The immature blur processing of the children is in line with others who have also found that children do not have other adult-like visual behaviors, such as contrast sensitivity, (Bradley and Freeman 1982) by 8 years of age.

5.4 The Impact of Cognition on Accommodative Accuracy and Stability

The impact of cognitive effort on accommodative behavior was investigated in Chapter 4. Our results suggest that children accommodated more accurately by approximately 0.23 D (average between Group1 and Group 2) when performing a task requiring more cognitive effort than just passively viewing a task (Table 4.2). The adults did not have a difference in accommodative accuracy between the two tasks. Not only was accommodative accuracy in children impacted by cognition, but as discussed above, the accommodative response was also more stable in both the time and frequency domains as RMS and LFC decreased significantly in the children and the adults when comparing the passive and active viewing tasks (Table 4.2), with the largest impact being in the youngest children in Group 1.

5.5 The Impact of Time on Accommodative Accuracy and Stability

Prior to the work in this dissertation, accommodative accuracy and stability had yet to be studied over a testing period greater than 30 seconds in children. One concern with a task with an increased duration of time is that children with greater amounts of hyperopia may be unable to sustain an adequate accommodative response throughout the task. The results of Chapter 4 however, suggest that accommodative accuracy and accommodative stability were only affected over time in the passive viewing condition as the response decreased significantly over time in the youngest children with the greatest amount of hyperopia while RMS increased significantly over time in the older children during the passive viewing task. Even though significant changes in time were found in lag (Group 1 and 2 passive condition) and RMS (Group 2 passive condition), it should be noted that the model suggested that the change in lag for a +3.50 D SE child with uncorrected hyperopia only had a significant change in lag of ≤ 0.25 D, while an older child would have been predicted to also have an increase in RMS of 0.10 D over the course of the experiment, both of which may not be clinically meaningful changes.

5.6 The Impact of Uncorrected Hyperopia on the Results of the Experiments

Other studies have shown that children with increased levels of uncorrected hyperopia may be exposed to increased levels of defocus (Mutti 2007, Candy, Gray et al. 2012, Tarczy-Hornoch 2012), which may negatively impact their visual experience. The underlying purpose of the work of this dissertation was to determine if children with greater amounts of uncorrected hyperopia experienced greater amounts of accommodative lag or accommodative instability while performing near visual tasks. A major limitation of the current work is that only 4 children were recruited with uncorrected hyperopia of the most plus eye (SE) > +3.50 D. Thus, the results of this work should be cautiously applied to children with greater amounts of hyperopia. The results from this work in regards to SE are summarized in Table 5.3. Despite the limited number of subjects with larger amounts of uncorrected hyperopia in the study, uncorrected hyperopia was found to be independently associated with increased accommodative lag and increased RMS under sustained viewing in the passive condition (Table 4.3). Increased SE was also associated with increased RMS in in the blur detection experiment of Chapter 3.

In regards to visual experience, while SE was not found to be independently associated with blur detection thresholds when RMS was included in the multivariable model (Table 3.2), given that SE was significantly correlated with blur detection thresholds in the univariable analysis and SE was significantly associated with increased RMS, it is feasible that the impact of SE on blur detection thresholds is mediated through RMS. Currently, the relationship is speculation and more work needs to be done to understand the complex relationships between refractive error, accommodative behavior and visual experience.

TABLE 5.3 Summary of the adjusted regression analysis of accommodative lag (passive and active viewing conditions) and RMS (blur detection threshold, passive and active) regarding the most plus SE performed throughout the dissertation. Significant p-values for most plus SE are reported in bold. (Note: the blur detection threshold and sustained studies had different variables in the models specific to the hypothesis of the respective experiments. Blur detection threshold multivariable analysis included variables SE, age and accommodative lag, while the passive and active analysis included variables SE and stimuli viewed (shape vs. Letters/text. Additionally, 95% CI were removed from the table for simplicity).)

		Blur Detection Threshold			Passive		Active	
		Beta-coeff	p-value		Beta-coeff	p-value	Beta-coeff	p-value
Accomm Lag	**Intercept**	-	-	**Intercept**	1.83	<0.001	1.71	<0.001
	SE	-	-	**SE**	0.13	**0.042**	0.05	0.292
	Stimuli	-	-	**Stimuli**	-0.34	0.018	-0.33	0.008
RMS	Intercept	0.32	<0.001	**Intercept**	0.68	<0.001	0.37	<0.001
	SE	0.05	**<0.001**	**SE**	0.07	**0.002**	0.02	0.063
	Age	-0.001	0.942	**Stimuli**	-0.19	<0.001	-0.06	0.063
	Lag	-0.06	0.035					

It is clear from Table 5.3 that the relationship between SE and accommodative lag and RMS is quite variable across conditions, suggesting that while sometimes individuals with increased amounts of uncorrected hyperopia have a greater lag of accommodation or greater accommodative variability, other times their accommodative behavior is similar to children with lesser amounts of hyperopia. In summarizing the accommodative behavior as a function of uncorrected hyperopia, while the relationship is not always significantly positively correlated, we did not find a negative correction in the analyses. Thus, if children with uncorrected hyperopia are to have a larger lag or increased variability in their accommodative response, it will most likely be those children with larger amounts of uncorrected SE rather than those children with lesser amount of uncorrected hyperopia.

5.7 Possible Clinical Significance

Previous studies have described significant associations between larger amounts of uncorrected hyperopia and poorer academic performance in the absence of strabismus and amblyopia (Grisham and Simons 1986, Rosner and Rosner 1987, Rosner and Rosner 1997, Williams, Latif et al. 2005). There are also case reports in the literature that describe positive effects of prescribing spectacles for some patients with uncorrected hyperopia (Dwyer and Wick 1995, Cotter 2007), but the evidence is lacking in terms of randomized clinical trials. One hypothesis to explain the associations between decreased academic performance and increased uncorrected hyperopia and the improvement in academic performance that may occur due to wearing spectacles, is that while the hyperopic refractive error is uncorrected, the increased accommodative demand for near work may impact the child's ability to learn and perform in school if the children are unable to generate an adequate accommodative response both in terms of accuracy and stability. While we did find some occasions for which children with increased uncorrected hyperopia had increased accommodative lag and increased accommodative variability, as mentioned above, the findings were not consistent across experimental conditions (Table 5.3).

While increased levels of uncorrected hyperopia have been associated with poor academic performance, association should not be interpreted as causation. In order to differentiate between the cause and effect of the association between uncorrected hyperopia and poor academic performance, more research needs to be completed. First, it important to consider that decreased image quality was not directly measured in this study or the others mentioned, but rather decreased image quality is inferred due to the observed increase in measured defocus. Actual image quality needs to be measured in children with uncorrected hyperopia who have increased lags of accommodation or increased accommodative variability to better understand their visual experience. Also, randomized clinical trials are needed to understand the impact that reducing accommodative demand would have on the accommodative response and any influence on academic performance.

In addition to investigating accommodative lag and accommodative variability in a number of experimental conditions, the relationships and associations between blur detection thresholds and independent variables RMS, age, SE and accommodative lag were also explored in this dissertation as blur detection thresholds have not been determined in children with uncorrected hyperopia. The results of Chapter 3 demonstrated that increased blur detection thresholds are associated with increased RMS, increased SE, and younger age in univariable analyses. Mean accommodative lag was not found to be significantly associated with blur detection thresholds. In multivariable analysis, RMS and age were found to be independently significant when controlling for the other independent variables whereas SE and accommodative lag were not found to be significantly associated with blur detection thresholds in the model. However, as mentioned above, SE may impact blur detection thresholds through RMS. Nevertheless, the results suggest that further study is warranted given the significant associations detected in both the univariable and multivariable exploratory analyses.

5.8 Future Research Directions

This dissertation has shown that accommodative microfluctuations may arise from both sensory and motor mechanisms as we observed that accommodation became more variable with both an increase in the accommodative lag and an increase in accommodative response. The sensory mechanism is likely to act as part of the accommodative control mechanism as changes in luminance and contrast (Campbell, Robson et al. 1959, Gray, Winn et al. 1993), and pupil size (Campbell, Robson et al. 1959, Gray, Winn et al. 1993) have been shown to effect the magnitude of the microfluctuations. In Chapters 2 and 4 we found that microfluctuations were greatest in the experimental conditions in which the accommodative lag was greatest. While the influence of accommodative lag on microfluctuations in terms of an accommodative control model is not understood, it may be that microfluctuations increase as an attempt for accommodation to have deliberate correction toward the target. More investigation needs to be done to better understand the accommodative control model in terms of microfluctuations and accommodative lag.

The role of the motor mechanism in accommodative microfluctuations is even less understood. Campbell et al. (1959) suggested that the microfluctuations may occur due to "tremor" in the muscular system of the eye that may be part of the sensory feedback loop (Campbell, Robson et al. 1959). Their hypothesis is in line with other sensory and motor systems in the body that have been shown to be related to central nervous system oscillations that manifest in peripheral muscle systems and are thought to be part of a feedback loop for muscle stability (McAuley and Marsden 2000). Kotulak and Schor (1986) have also suggested that microfluctuations may be influenced by noise in the accommodative plant as tension on the lens zonules change with changes in accommodative effort (Kotulak and Schor 1986). While there are many hypotheses generated to explain the underlying motor contribution to accommodative microfluctuations, scientific evidence in support of the motor hypotheses is still lacking and thus more research is needed.

The work of this dissertation was focused on accommodative lag and accommodative variability in children with uncorrected hyperopia. One of the most obvious concerns in individuals with increased accommodative lag and increased accommodative variability is that they may experience decreased retinal image quality, which may impact their daily activities such as learning and school-work. However, is it important to consider that neither the work of this dissertation nor the work of others who have measured increased accommodative lags as a function of uncorrected hyperopia (Ingram, Gill et al.

1994, Mutti 2007, Candy, Gray et al. 2012, Tarczy-Hornoch 2012) have demonstrated a direct measurement of image quality. A decrease in retinal image quality has been inferred with the underlying assumption that an increase in defocus (accommodative lag) results in a decrease in image quality. There is however, some evidence that questions the underlying assumption that accommodative lag equates to blur. Roberts et al. (2015) has demonstrated that even with an increase in accommodative lag at higher accommodative demands, subjects did not report change in the clarity of the stimulus unless the accommodative gain decreased below 70%, on average (Roberts, Anderson et al. 2015). Sreenivasan et al. has also shown that an increase in accommodative lag does not always result in a decrease in retinal image quality in myopic subjects (Sreenivasan, Aslakson et al. 2013).

Similar to the assumption that an increase in accommodative lag results in an increase in defocus, one could assume that an increase in accommodative variability would likely result in increased defocus. However, providing the accommodative microfluctuations fall within the DOF, an individual would not experience a change in the perception of stimulus clarity. The difficulty is that it is unknown whether or not the microfluctuations fall within the DOF of the individual, especially in children, as DOF was shown to be difficult to measure in the pediatric population. Thus future studies of accommodative lag and accommodative variability need to be directed at understanding real time retinal image quality along with simultaneous measures of the individual's perception of stimulus clarity.

The results of Chapter 3 warrant future studies into blur detection thresholds. While this study has shown that higher levels of blur detection thresholds are associated with increased RMS, it was also shown that increase RMS was associated with an increase in SE. Thus, it is unknown whether the increased blur detection thresholds are simply due to increased levels of retinal image instability or if perhaps the associations are secondary to neural deficits regarding blur detection in individuals with increased levels of hyperopia given that increased RMS is significantly associated with increased uncorrected SE. Thus, it is important to gain an understanding in the relationship between blur detection, RMS and SE as it is feasible that SE influences blur detection through RMS.

In terms of refractive error development, infants are typically born hyperopic and then undergo emmetropization, a process in which refractive error changes in the emmetropic direction (Cook and Glasscock 1951, Mayer, Hansen et al. 2001, Mutti 2007). Previous studies suggest that infants who are able to overcome their hyperopic defocus through accommodation successfully undergo the emmetropization process, whereas the infants who do not accommodate are less likely to emmetropize (Ingram, Gill et al. 1994, Mutti 2007). The question remains, however, why do some infants accommodate through their hyperopia whereas others do not? Perhaps the answer lies in the function of the individual infant’s afferent and efferent visual pathways. If the afferent system was intact but a neural deficit existed in the efferent system, either in motor control or the accommodative plant itself, blur would be detected but a motor response would not be generated. However, based on previous studies of accommodation and emmetropization in infants, one could assume that the deficiencies are not likely to be efferent in nature. While infants and young children with larger amounts of hyperopia tend to under-accommodate relative to a given accommodative demand, they do accommodate, just not to the same accuracy as individuals with lesser amounts of hyperopia. Our data suggests that at least by three years of age, children had similar accommodative responses when looking from a distance to near stimulus despite having a large range of uncorrected hyperopia, suggesting the efferent pathway is functional, even in the children with larger amounts of hyperopia. The children in our study were > 3 years of age and thus it is not possible to know what their blur detection ability or accommodative behavior were like when they were infants. Perhaps a more convincing argument that the infants with larger amounts of hyperopia likely do not have a deficit in the motor response, even during infancy, is that none of the children in this study had previously worn correction for RE, and yet they had normal visual acuity with no evidence of amblyopia. Thus, presumably the children with larger magnitudes of hyperopia in this study also had similar magnitudes of hyperopia as infants and thus accommodated at least a portion of the time to experience clear vision and avoid amblyopia from prolonged exposure to retinal defocus. Despite the large accommodative demands, population-based data showed that > 80% of children aged 36 to 72 months with bilateral uncorrected hyperopia greater than +3.50DS who did not emmetropize also did not have decreased bilateral visual acuity (Tarczy-Hornoch, Varma et al. 2011), suggesting they are able to detect blur and accommodate. If a neural deficit were to exist in the afferent pathway, however, individuals may have a deficit in deciphering blur, which could result in a deficient motor response (increased RMS) in the responding efferent system given that blur is known to drive the accommodative response (Heath 1956, Schor 1985, Mays and Gamlin 1995) (Heath 1956, Schor 1985, Mays and Gamlin 1995, Tarczy-Hornoch, Varma et al. 2011) and has been shown in Chapter 2 of this dissertation. If a neural deficit in blur detection was present during the first year of life when the majority of emmetropization occurs, it could explain why higher amounts of hyperopia persist in some children.

This study suggests that the sensory theory of emmetropization warrants further exploration as the results in this study can merely suggest that a sensory blur detection deficit may exist in children with increased amounts of hyperopia by 3 years of age. Anecdotally, two of the four subjects with > +4.00 D SE returned to the laboratory 8-10 months after their initial laboratory visit. Subject 17 (4.4 yrs.) had +4.58 D SE in the most plus eye while Subject 36 (6.3 years) had +4.91 D SE in the most plus eye. Subject 36 was prescribed a partial plus spectacle correction at her initial visit while Subject 17 remained uncorrected. Both subjects participated in the blur detection threshold task and both subjects had minimal change in threshold values (Subject 17: 0.19 higher; Subject 36: 0.13 lower), despite Subject 36 having been wearing spectacle correction for the previous 10 months. While concrete conclusions cannot be arrived via these two subjects, the data do suggest that the sensory theory regarding decreased blur detection thresholds in individuals with increased amounts of hyperopia should be further investigated as it may have significant implications in the process of emmetropization and vision development.

Further studies need to be done to understand the role of accommodative microfluctuations in children with greater amounts of hyperopia and individuals with pathological conditions, such as strabismus and amblyopia. While we attempted to recruit subjects over a large range of hyperopia, we were only able to recruit 4 children with greater than +3.50 D SE and the maximum amount of uncorrected hyperopia we were able to recruit was +5.00D SE, thus more subjects are needed to characterize the accommodative behavior in children who have accommodative demands that are approaching their accommodative amplitudes during near activities (Anderson, Hentz et al. 2008). It has been shown that as the accommodative demand increases, the accommodative lag increases as well (Gwiazda, Thorn et al. 1993, Abbott, Schmid et al. 1998, McClelland and Saunders 2004, Anderson, Glasser et al. 2009, Roberts, Anderson et al. 2015), and thus individuals with greater amounts of hyperopia than we were able to recruit may show changes in their accommodative behavior, which may be even more prominent than what we were able to demonstrate in our work.

Additionally, while we excluded subjects with strabismus and amblyopia, children with uncorrected hyperopia are at risk for developing strabismus (Cotter, Varma et al. 2011) and amblyopia (Tarczy-Hornoch, Varma et al. 2011). It is thought that some children with high isometropic accommodative demands or high accommodative convergence/accommodation (AC/A) ratios are at risk for developing strabismus and amblyopia (Fawcett and Birch 2003), however, very little is known about their ocular motor control system, other than individuals with strabismus and amblyopia often times have larger accommodative lags in the amblyopic eye (Ciuffreda and Rumpf 1985, Manh, Chen et al. 2015). Thus, future studies should be aimed at understanding the ocular motor control mechanism in subjects both at risk for pathological conditions such as strabismus and amblyopia and those who already manifest the disease.

APPENDICES

Appendix A – PowerRef II Control Studies

A.1.1 Introduction

The instrument used for data collection for all studies was the PowerRef II (PR) (Plusoptix, Atlanta, GA). The PowerRef II is an infrared eccentric photorefractor which has the capability of collecting refractive error, pupil size and eye position at a distance of 1M from the subject, making it an ideal instrument for obtaining measurements from infants and young children (Howland, Dobson et al. 1987). The PR has two methods in which it collects data. It can be used in static mode where the PR collects binocular sphere/cylinder and axis refraction and pupil size, or it can be used in dynamic mode where it collects refractive error in the vertical meridian of the eye, as well as pupil size and eye position at a sampling rate of 25 Hz in both eyes simultaneously. The light source of the PR is made up of multiple light emitting diodes (LEDs). Optical defocus of the eye is measured from the luminance gradient of light from the source exiting the pupil after it has traveled through the eyes optics to the retina where it is reflected back towards the light source (Roorda, Campbell et al. 1997). The use of multiple LEDs allows for an increased operating range of over which the refractive error can be measured (Bobier and Braddick 1985, Roorda, Campbell et al. 1997). Pupil size is determined using an edge detection algorithm while eye position is determined by comparing the location of the first purkinje image to the center of the pupil (Schaeffel, Wilhelm et al. 1993, Gekeler, Schaeffel et al. 1997, Choi, Weiss et al. 2000). The manufacturer recommends that refractive error measures outside of -7.00 D and +5.00 D, pupil size < 4 mm and > 8 mm, and eye position outside of 10º horizontally and 5º vertically are outside of the operating range of the PowerRef II and thus unreliable (Plusoptix).

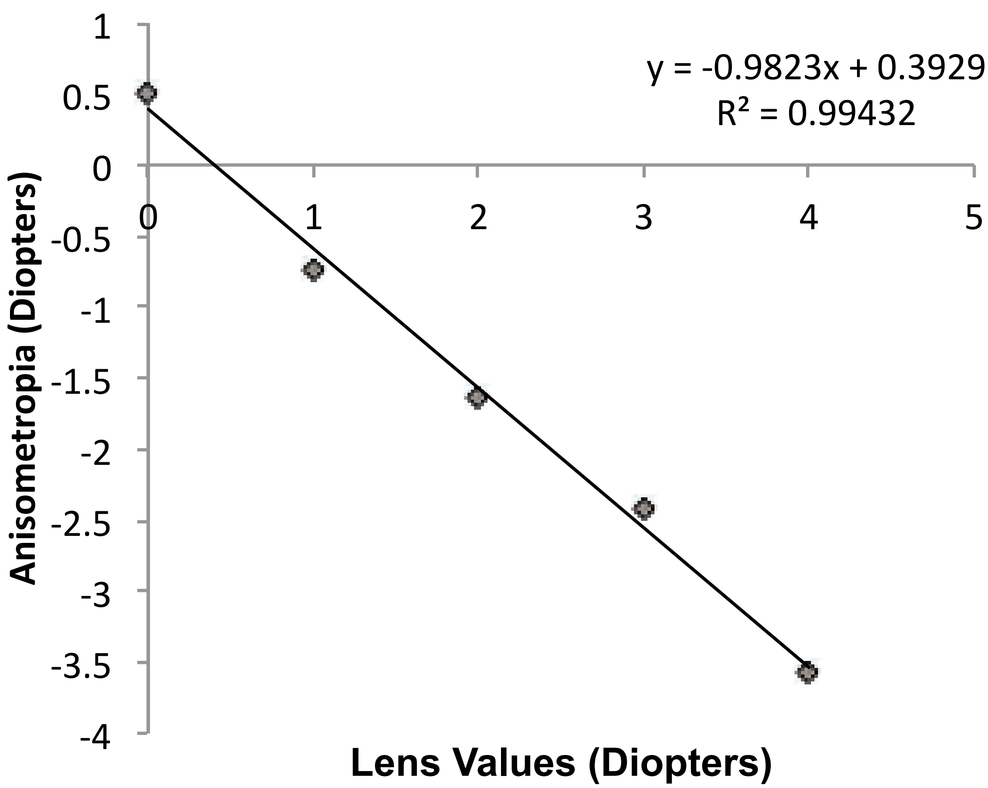
It is important to fully understand any limitations of the instrumentation used to collect data, as some limitations may affect the accuracy and reliability of the results obtained throughout the data analysis process. Therefore, several control studies were performed on the PowerRef II to identify possible sources of variability in the data that come from the instrument. The control studies were aimed at identifying the repeatability of the measures of the instrument as well as confirming the manufacturer's recommendations regarding the effects that off-axis viewing, and changes in pupil size may have on the measures of refraction. Additionally, the effects of differing retinal luminance on refractive error measures was investigated.

Several adult subjects were asked to participate in the control experiments. Not all subjects participated in all studies. Subjects who participated in the control experiments did not receive vision examinations and had normal vision by self-report.

A.1.2 Refractive Error Calibration

Prior to data analysis, each individual underwent a trial lens calibration for each eye to obtain more precise measures of refractive error (Schaeffel, Wilhelm et al. 1993). For the calibration, the eye being calibrated was occluded with a Kodak 89B Wratten gelatin filter that blocked visible light while transmitting infrared light, enabling the PR to obtain measures of the eye occluded by the Wratten filter. The fellow eye fixated a distance letter that subtended 0.21º at 16.5 feet. The calibration consisted of refractive error measures with only the filter in place, as well as four additional measures by placing trial lenses of known powers (+1 to +4 D in 1 D steps) in front of the occluded eye for 5 seconds, thus allowing for the luminance profile across the pupil to change without eliciting an accommodative response. Because the calibration was performed on non-cyclopleged eyes and the subjects had uncorrected hyperopia it was feasible that the fixing eye's accommodative response could vary during the trial, which could lead to erroneous measures of refraction of the eye being calibrated due to consensual accommodation. Thus, rather than using the induced (from the lens) mean of the raw refractive error values of the eye being calibrated to obtain the calibration slope, the difference between the induced mean refractive error values of each eye (anisometropia) were used to account for any changes in accommodation. To obtain the calibration slope, the lens power was plotted graphically on the x-axis while the change in anisometropia was plotted on the y-axis and linear regression analysis was performed. Subjects were required to have a minimum of 4 calibration data points to generate the regression line in order to be included in any accommodative analyses. An example of the plotted lens power and anisometropia are shown in Figure A1.

FIGURE A.1.1 Sample plot of the regression analysis used to determine the calibration slope for one subject. The x-axis represents the lens values used for the calibration (the first value of 0 was when no lens was in place). The data on the y-axis represents the induced mean anisometropia measured between the two eyes when each trial lens was in place. The slope of the regression line represents the calibration slope that was applied to the refractive error data of the respective eye.



A.1.3 Control Studies Data Analyses

Repeatability of refractive error and eye position was evaluated using the within-subject standard deviation (Sw) and the intra-class correlation coefficient (ICC). Sw was calculated as the square root of the variance across subjects and thus a lower Sw value suggests higher repeatability (Bland 2015). The ICC was calculated using the following equation,

between-subject variance/between-subject variance + *within-subject variance.*

An ICC equal to 1 suggests no variance exists within repeated measurements, thus a higher ICC value is representative of good repeatability. The ICC scale is categorized as follows: > 0.90 = good; 0.75 to 0.90 = moderate; 0.40 to 0.75 = fair; < 0.40 = poor (Fleiss 1986). Instrument tolerance to changes in off-axis viewing, retinal luminance and pupil size are reported descriptively.

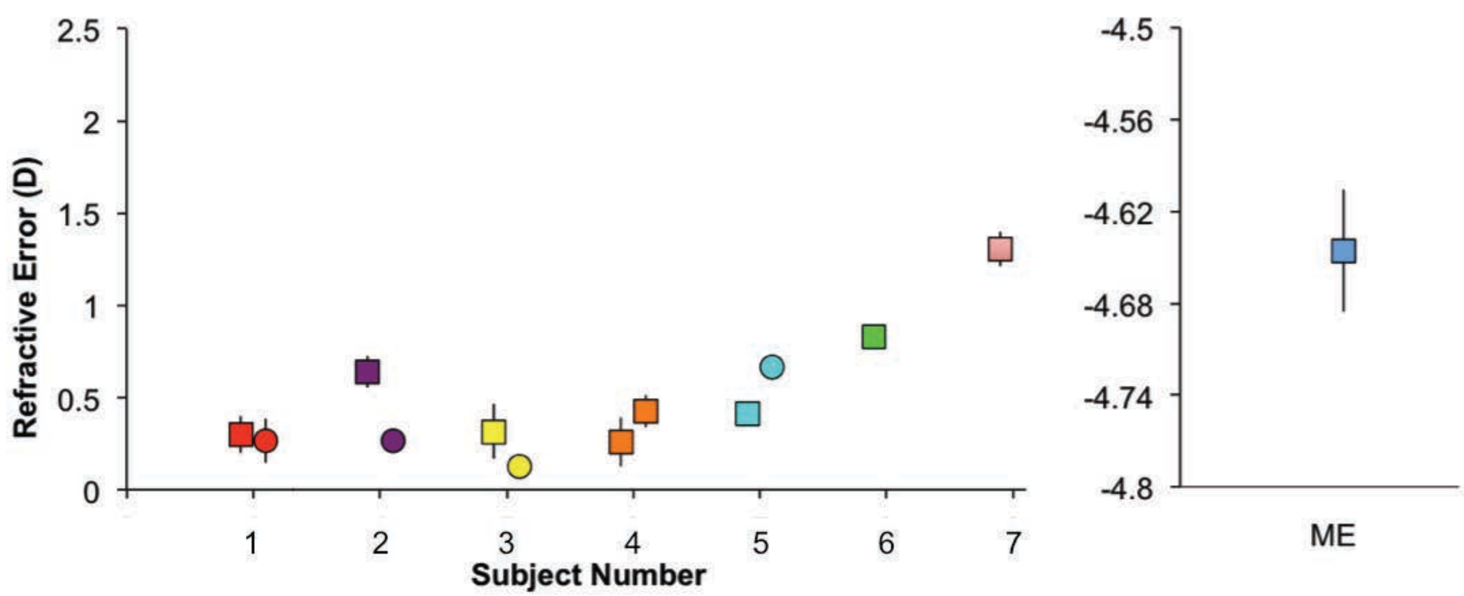
A.1.3.1 The Repeatability of Refraction and Vergence Measurements

Repeated measures of dynamic refraction (25 Hz) were taken on one model eye (RyuSyo Industrial Co., Ltd. Hiroshima, Japan, Model S/N-AS0105, -4.50 D), with a fixed pupil size of 5 mm and seven subjects (two presbyopes (47-63 years) and five adult, non-presbyopes (29-39 years). Initially 9 subjects were recruited but two subjects were excluded from repeatability analysis for refractive error due to one having uncorrected hyperopia and the other having a cataract. Subjects viewed a 20/50 sized letter presented on an M&S SmartSystem (M&S Technologies, Inc. Niles, IL) calibrated for 16.5 feet (0.21° visual angle). The PowerRef II was placed 1 M directly in front of the subject. The subject was aligned to fixate a distance 20/50 letter such that their line of sight was 4.5 cm above the center of the PowerRef II. The subject viewed the stimulus for 5 seconds and the task was repeated ten times on each subject as well as the model eye.

A.1.3.1.1 The Repeatability of Refractive Error Measures

The mean and root-mean square (RMS) values were calculated to determine the overall average measure of refraction as well as the variability (RMS) of refractive error during each trial. Refraction of the right eye was obtained from all seven subjects however, refraction of the left eye was obtained from only five of the subjects (one subjects' pupils were < 4 mm and one subject did not have a calibration of the left eye). The average refractive error measured for the model eye over the ten trials was -4.65 D, while the range of the subject's refractive error over the ten trials was +0.008 D to +1.47 D in the right eye and +0.02 D to +0.72 D in the left eye (Figure A2). The average variability of refractive error across the ten trials for the model eye was 0.04 D, while the average variability for subjects was higher with a mean intra-subject variability 0.11 D for both the right eye and left eye, (represented by error bars in Figure A2). For repeatability of the mean refractive error, the Sw value for the right, left and model eyes were 0.10, 0.07 and 0.04 respectively. The ICC for the right and left eyes were both 0.99.

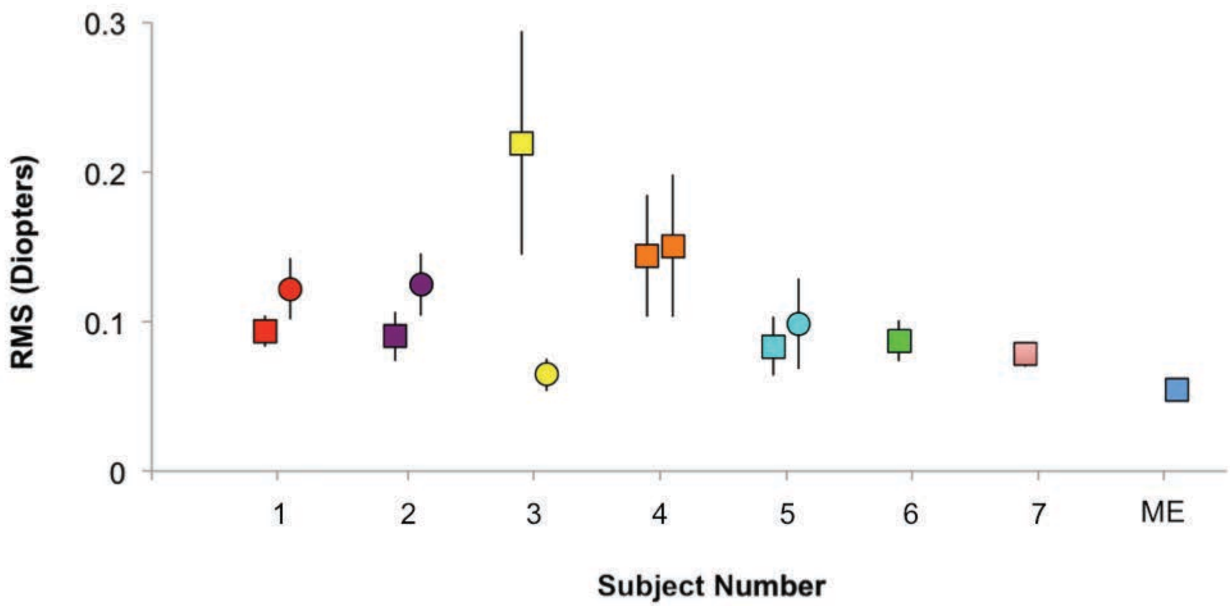
FIGURE A.1.2 Mean refractive error values for the right (squares) and left (circles) eyes of the 7 subjects and model eye (ME) for the 10 repeated trials. Error bars represent the standard deviation of the mean refractive error across the 10 trials. (Note: the y-axis for the model eye differs from the axis of the subjects due to the large difference in mean refractive error values of the subjects.)



The mean RMS for the 10 measures of the model eye was 0.054 (*SD* ± 0.003 D, minimum = 0.049 D, maximum = 0.059 D), while the intra-subject RMS for all ten measures was slightly larger at 0.11 D (*n* = 7, *SD* ± 0.03 D, minimum = 0.08 D, maximum = 0.22 D) in the right eye and 0.11 D (*n* = 5, *SD* ± 0.03 D, minimum = 0.06 D, maximum=0.15 D) in the left eye of the subjects (Figure A3). For RMS repeatability, the Sw value for the right, left and model eyes were 0.033, 0.028 and 0.003 respectively. The ICC for the right and left eyes were 0.93 and 0.94, respectively. The low Sw values in conjunction with the high ICC values indicate the PR has excellent repeatability in both the model eye and human subjects. Additionally, the variability in the measures obtained from the model eye, both for average refractive error and RMS values, likely represent the variability in the data that comes directly from the PowerRef II, suggesting that any additional variability in the data is likely to come from the subjects themselves (i.e.: accommodative variability, unstable tear film, head movements, etc.).

The repeatability of refractive error and accommodative variability measures was also used to obtain a cut-off value to be used to determine changes in refractive error and RMS in individuals between conditions as described in Chapter 2. The cut-off values for each measure was considered to be 3 standard deviations from the group mean. The calculated cut-off values for refractive error and RMS of the right eye were 0.27 D and 0.08, respectively.

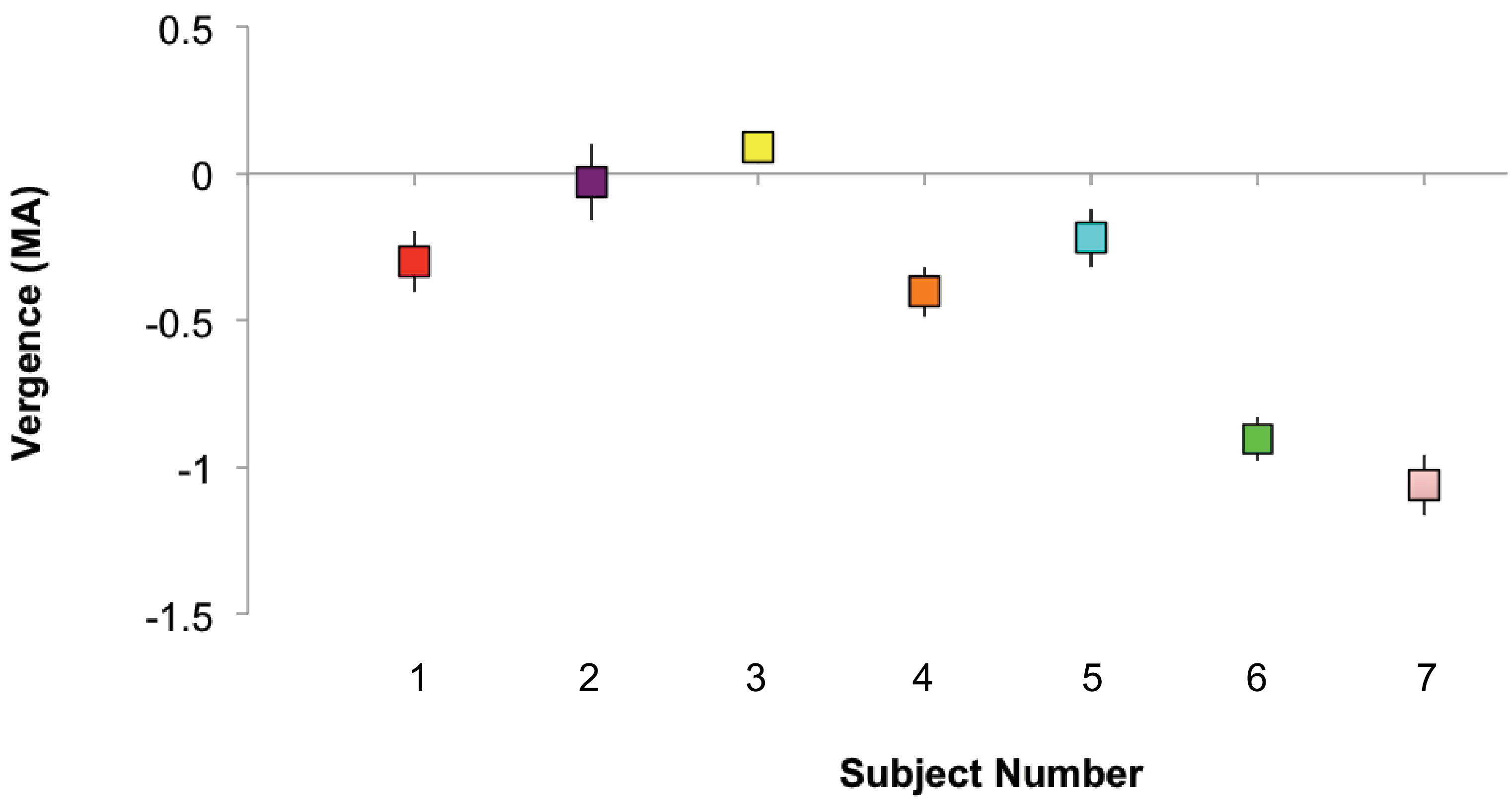
Figure A.1.3 Root mean square (RMS) values for the right (squares) and left (circles) eyes of the 7 subjects and a model eye (ME). Each value represents the mean RMS of 10 repeated trials. Error bars represent the standard deviation of the mean RMS across the 10 trials.



A.1.3.1.2 The Repeatability of Eye Position Measures

The PowerRef II measures gaze position in millimeters (mm) from the center of the pupil to the first purkinje image with the output file providing both gaze position of each eye in millimeters as well as in degrees using the Hirschberg conversion factor of 1mm=11.8º. Using the same data files from the refractive error repeatability analysis above, gaze position in degrees was converted offline to measures of vergence in meter angles (MA) using the subject's interpupillary distance as obtained by the PR. The mean vergence measures across the ten trials for each individual subject are shown in Figure A4. The mean intra-subject variability (standard deviation) for the 10 trials (denoted as the error bars in Figure A4) was 0.09 MA (minimum = 0.06 MA, maximum = 0.13 MA). The Sw value for vergence was 0.09 and the ICC value was 0.99 suggesting that the PR has excellent repeatability for vergence measures.

FIGURE A.1.4 Mean vergence measures for the 7 subjects across the 10 repeated trials. Error bars represent the standard deviation of the mean vergence measures across the 10 trials.

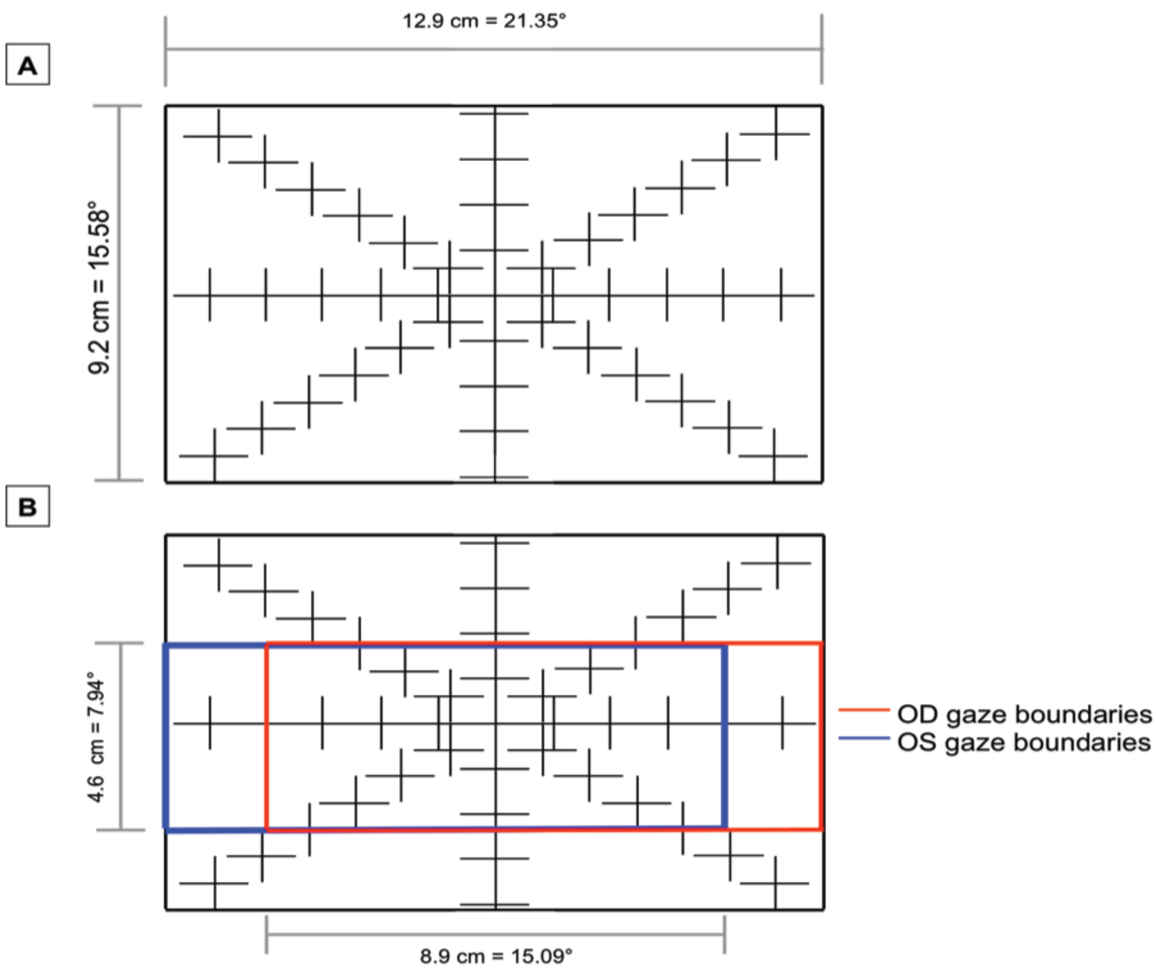


A.1.3.2 Instrument Tolerance to Off-Axis Viewing

The PowerRef II measures refraction based on the luminance profile in the vertical meridian of the pupil. Off-axis viewing may result in an elliptical pupil, which may introduce an erroneous luminance profile, thereby causing erroneous measures of refraction. The manufacturer suggests that the PowerRef II is accurate as long as the purkinje image is located within the pupil (personal written communication with manufacturer). However, the investigator wished to confirm this by determining the effect that off-axis viewing has on the refraction measures of six adult subjects as they viewed a 1.3 cm x 1.3 cm cross (viewing distance of 33 cm) at fixed horizontal and vertical off-axis viewing positions ranging from 15.58º vertically and 21.35º as seen in Figure A5a. The subjects viewed each stimulus position (33 positions total) for 5 seconds and the raw refraction values (REraw) were averaged during that time. The center position was viewed 13 times and the refraction was averaged over the 13 trials to obtain a baseline measure for each subject (BaseRE). Next, the magnitude that the refraction deviated (DevRE) from baseline was calculated by subtracting the BaseRE from the REraw value for each stimulus position for each subject. The mean and standard deviation of the absolute value of the DevRE for all six subjects at all 13 center positions was calculated. Any values outside of two standard deviations of the group mean DevRE for all subjects for the center viewing location were considered to be erroneous and were considered to be outside of the tolerable deviations for the experiments in the presented dissertation. The inner-most stimulus location for the horizontal (left and right), vertical (top and bottom) or diagonal (top and bottom) vectors that were identified as being greater than two standard deviations from the mean were considered to be the outer edge of the allowable stimulus window in the horizontal or vertical directions for the right eye (Figure

A5b denoted by red lines) and left eyes (Figure A5b, denoted by blue lines). As seen in Figure A5b, the over-lapping windows resulted in a maximum stimulus viewing area of 8.9 cm (15.09º) horizontally and 4.6 cm (7.94º) vertically. Despite these findings being used to identify the boundaries of the stimulus viewing area, systematic refraction changes with eye position were still observed in the experimental data and thus further steps were taken to correct for gaze position as detailed in Chapters 3 & 4.

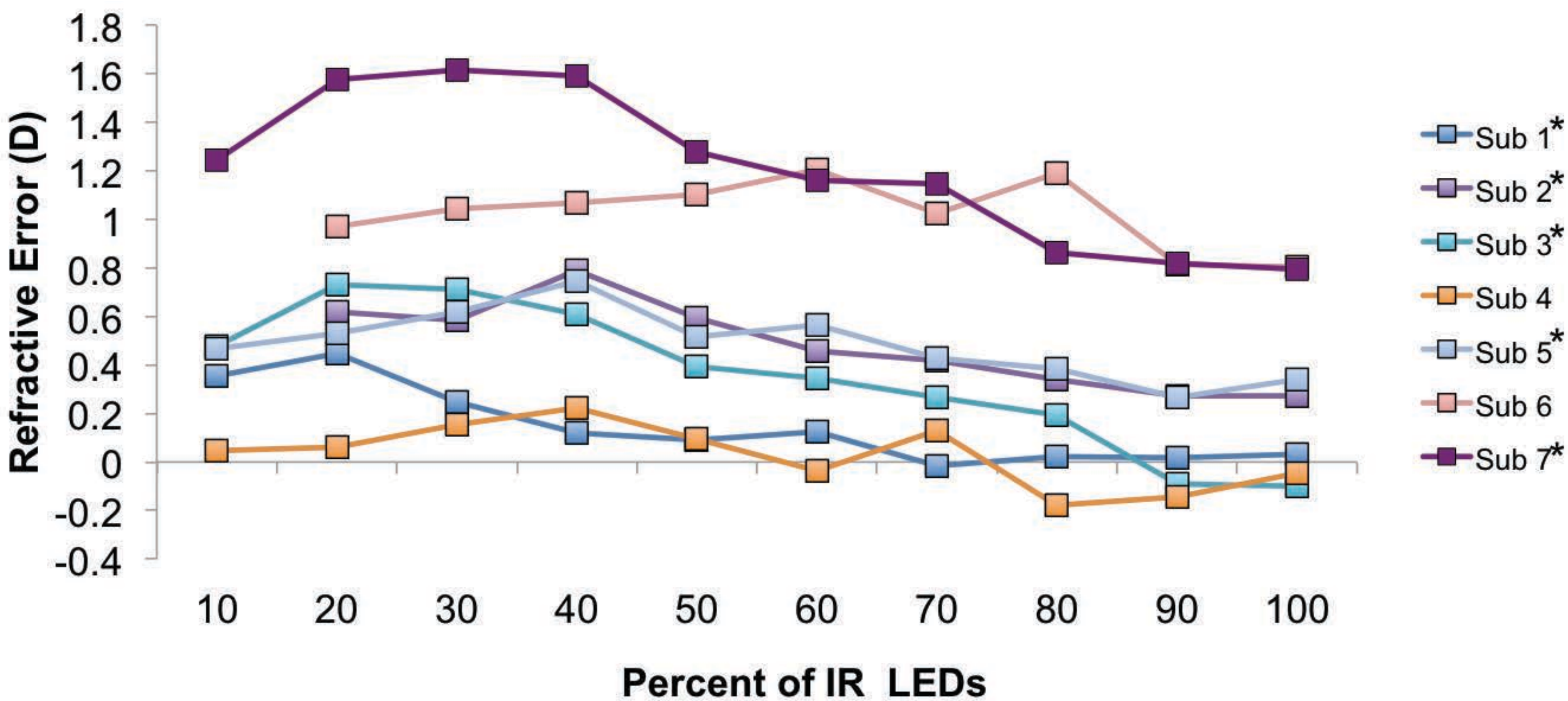
FIGURE A.1.5 A) The stimulus locations used to determine the stimulus viewing area. Each cross was separated by 1.1 cm (1.91°). Note that while all stimuli are shown in the figure, the stimulus crosses were shown to subjects one at a time. B) The red box represents the edges of the right eye's viewing window and the blue box represents the edges of the left eye's viewing window. The maximum stimulus size was determined to be 15.09° horizontal and 7.94° vertical.



A.1.3.3 Instrument Tolerance to Differing Retinal Luminance

The PowerRef II uses the calculated slope of retinal luminance across the pupil to determine refractive error. The PowerRef II has a built in feature to change the brightness of the LEDs (auto-brightness), thereby altering the amount of light able to be reflected. To determine the effects of the change in brightness on the refractive error measures, the auto-brightness mode was disabled and the brightness of the PowerRef II was increased in 10% increments from 10% brightness to 100% brightness, or until the PowerRef II was unable to take a measure due to light saturation in the pupil. As seen in Figure A6 most subjects' refraction declined as % brightness increased; six of whom were shown to have significant ($p < 0.05$) declines in refractive error measures using linear regression. On average, the subjects had a change of 0.60 ± 0.21 D across the range of brightness measured. The large fluctuations in refractive error suggest that enabling the auto-brightness function to be active during data collection may introduce significant levels of variability into the refractive error data. Thus, prior to the start of the calibration, subjects fixated the distance calibration stimulus and the auto brightness function was enabled to obtain the best brightness for their eyes as determined by the PowerRef II and then auto-brightness was disabled for all experimental data collection.

FIGURE A.1.6 The mean refractive error values for each brightness intensity measured for the right eyes of 9 subjects. The asterisks represent a significant ($p < 0.05$) change in slope across brightness intensities.



Additionally, while the brightness of the LEDs can be controlled manually by changing the percentage of brightness on the computer program that runs the PowerRef II, it is unclear if the displayed percentage of brightness actually corresponds to the intensity of the light (i.e.: does a 10% decrease as displayed on the screen represent a true 10% reduction of light intensity). A Minolta LS110 photometer (Minolta LS11, Ramsey, New Jersey) was used to measure the light intensity of the PowerRef II in megawatts (mW). The auto-brightness of the PowerRef II was set to manual mode and measured at 0 to 100% intensity, with increasing increments of 10%. This was repeated twice to obtain two measures at each level of intensity. The values from the two trials obtained at each % of brightness were averaged. The average brightness measured at 100% brightness was 17.40 mW and was considered the reference value and values obtained at all other intensities were divided by the reference value to determine the percent brightness (rounded to hundredth decimal point). The mean luminance at each brightness level is found in Table A1. The average percentages measured were all either equal to or within 1% of the expected value (based on the reference value) of the percent brightness manually selected on the software program, suggesting that the percent changes in brightness intensity displayed on the screen represents actual changes in brightness intensity to within 1%.

TABLE A.1.1 The mean light intensity measured (megawatts (mW)) of two repeated measures at each brightness level displayed on the PowerRef II are represented in the first two columns. The percentage of the light intensity (as referenced to the mean measured intensity at 100% brightness) is represented in the last column.

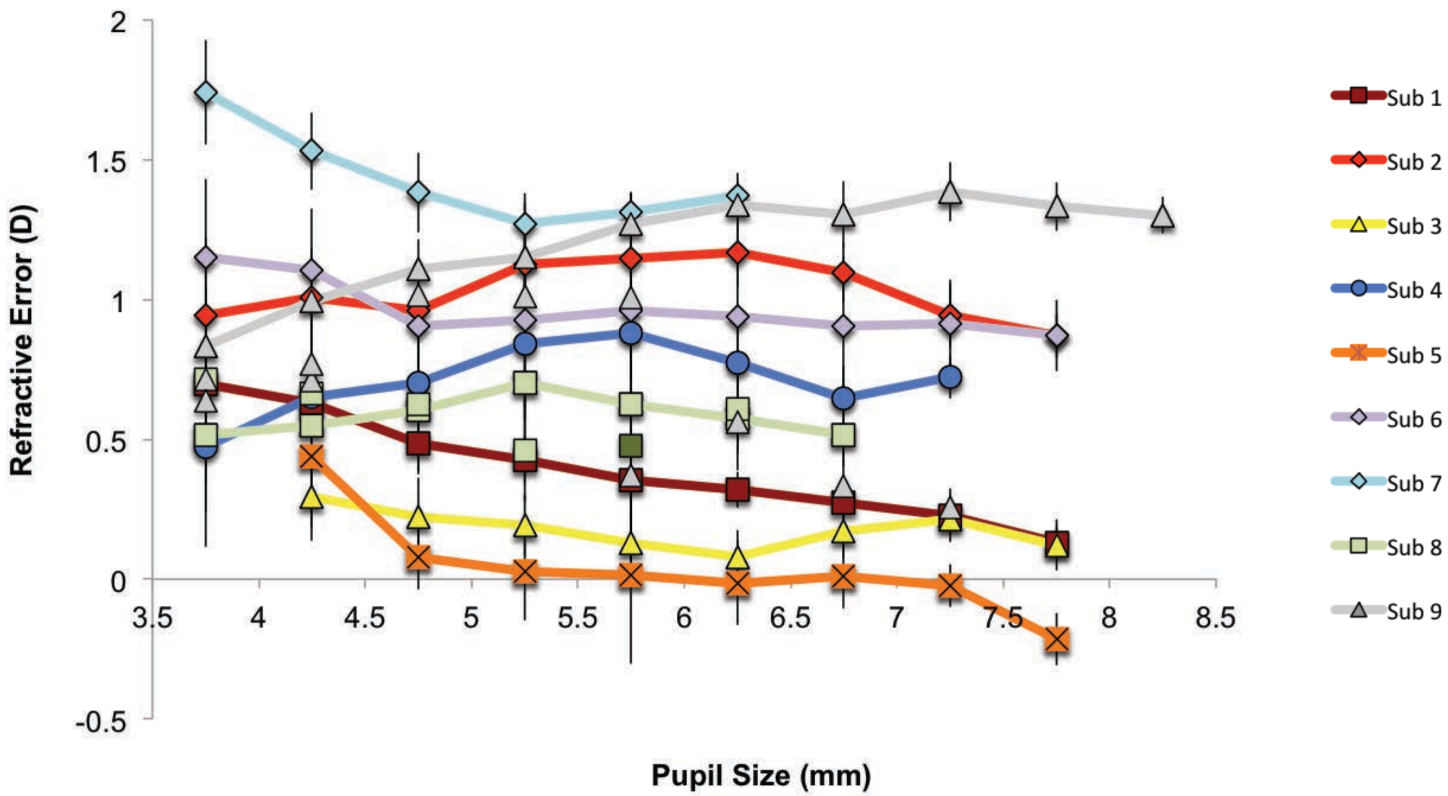
Brightness Displayed (%)	Mean Measured Light Intensity (mW)	Percentage of Calculated Brightness
100	17.400	100
90	15.76	91
80	14	81
70	12.3	71
60	10.4	60
50	8.65	50
40	6.85	39
30	5.07	29
20	3.38	19
10	1.685	10
0	0.0575	0.00

A.1.3.4 Instrument Tolerance to Change in Pupil Size

Pupil size is known to impact measures of refraction with infrared photorefraction techniques (Bobier and Braddick 1985, Gekeler, Schaeffel et al. 1997) and thus it is critical to understand the impact of pupil size on the precision of the PowerRef II measurements. The manufacturer suggests that refractive error data collected on pupils less than 4 mm or greater than 8 mm is not reliable. To confirm the manufacturer's suggested values for reliable pupil ranges (4 - 8 mm), refractive error was measured on eight subjects; one presbyope, and seven non-presbyopes. The seven non-presbyopic subjects were cyclopleged using 1% cyclopentolate to paralyze accommodation. The presbyopic subject was not cyclopleged. The subjects viewed a 20/50 letter at 16.5 feet (as described above under section 1-*repeatability of refraction and vergence*) with the right eye monocularly. For the presbyopic subject, the room lighting was turned down in order to achieve maximum pupil size without the use of mydriatics. The subject held a felt cloth between her two eyes to act as a septum while the investigator systematically introduced light from a transilluminator from the side of the subject's head directly into the pupil of the subject's left eye resulting in direct pupil constriction of the left eye and consensual pupil constriction of the right eye. The light was then moved away from the line of sight resulting in direct and consensual pupil dilation. The procedure was repeated several times and performed slowly to allow the PowerRef II to take numerous measures at various pupil sizes for analysis. For non-presbyopic subjects, the effect of pupil size was determined by cyclopleging the subject and then having them fixate the same distant 20/50 letter target described above with the right eye while the left eye viewed the fixation point through a variable aperture, which allowed pupil size to be manipulated. Refraction and variability (RMS) was evaluated as a function of pupil size.

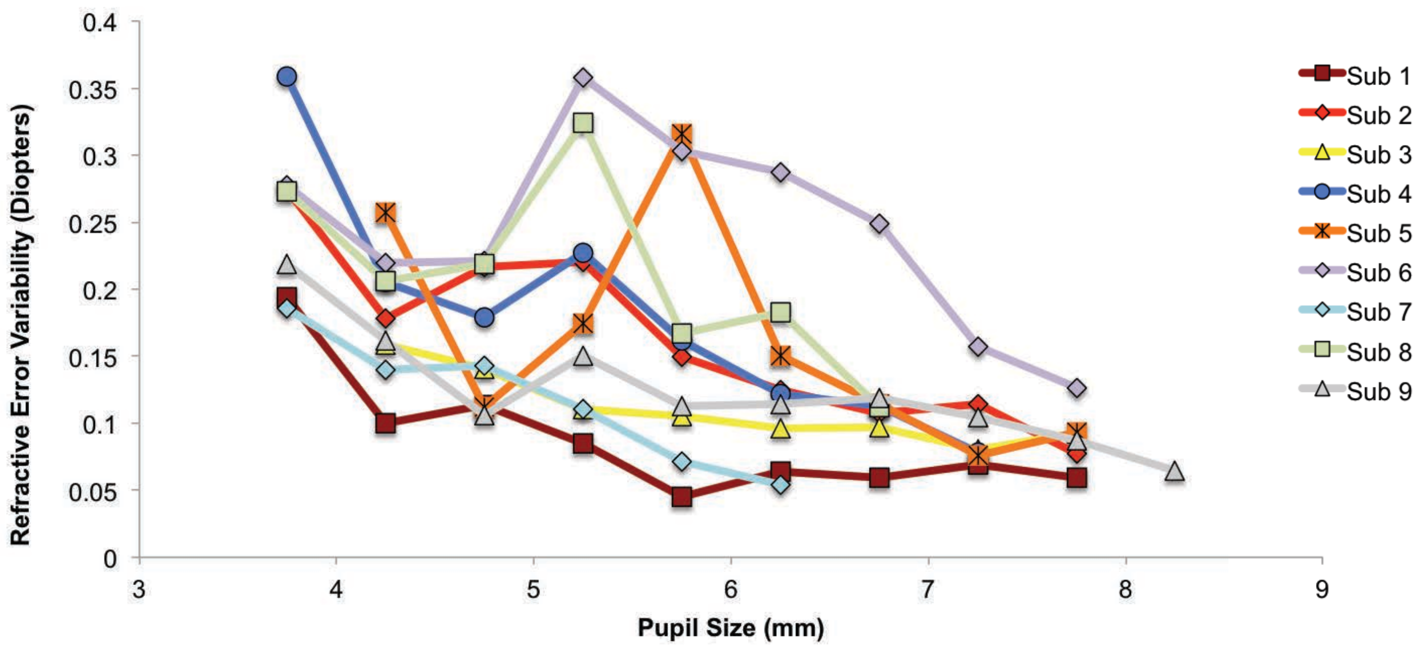
Pupil size was binned into 0.5 mm bins from 3.5 mm to 8.5 mm (3.5 to < 4.0, 4.0 to < 4.5, 4.5 to < 5.0, 5.0 to < 5.5, 5.5 to < 6.0, 6.0 to < 6.5, 6.5 to < 7.0, 7.0 to < 7.5, 7.5 to < 8.0, 8.0 to < 8.5 mm). Using linear regression pupil size was not determined to be a significant predictor for refractive error within the manufacture's recommended range of pupil size (4 mm to 8 mm) in all but two subjects (Sub 1 and Sub 5). Despite the two subjects with a significant decrease in refractive error, Figure A7 demonstrates that across subjects, pupil size had no systematic effect on the mean refractive error measures. The refractive error measures were again binned into 0.5 mm pupil size bins and the variability (RMS) of refraction within each bin was analyzed as a function of pupil size.

FIGURE A.1.7 The mean refractive error values for the right eyes of the 9 subjects for each pupil bin (bins are 0.5 mm in size). Pupil size was altered by using a variable pupil aperture in front of the eye with the size being continuously manipulated by the investigator via a lever.



A detailed inspection of Figure A1.8 reveals that while the RMS is smaller for the largest pupil measured for each subject, the changes in RMS with respect to pupil size are not necessarily linear as several subjects experienced an increase in RMS in the mid-pupil range. Therefore, considering results of both the average refraction data as well as the RMS data, all analysis for the experimental conditions will only exclude pupil sizes < 4.00 mm and > 8.0 mm as recommended by the manufacturer.

Figure A.1.8 The mean RMS refractive error values for the right eyes of the 9 subjects for each pupil bin (bins are 0.5 mm in size). Pupil size was altered by using a variable pupil aperture in front of the eye with the size being continuously manipulated by the investigator via a lever.



A.1.4 Summary

The results of the control experiments demonstrate that the PR is a reasonable instrument to collect the refractive error data used in this dissertation provided the data exclusion criteria are utilized as suggested based on the results of the control experiments and recommendations of the manufacturer, with the exception of gaze position. Despite performing the control study for the stimulus window size as well as using the recommendations from the manufacturer regarding eye position, a correction factor was needed for experiments in Chapters 3 and 4. Further control studies need to be performed to understand the relationship between the changes in refractive error that correlated with eye position for future study designs.

Appendix B. Subject Experiment Participation Summary

TABLE B.2.1 Summary of subjects' age, mean cycloplegic refractive error as obtained by the Grand Seiko autorefractor, and visual acuity for each eye as measured by HOTV.

Subject	Age	OD Refractive Error	OD VA	OS Refractive Error	OS VA
1	5.5	+ 3.16 -1.12 X 177	20/ 25	+ 3.71 -0.99 X 178	20/ 20
2	4.3	+ 1.90 -0.26 X 079	20/ 25	+ 2.00 -0.41 X 086	20/ 25
3	5.2	+ 1.36 -0.85 X 173	20/ 32	+ 1.80 -0.34 X 088	20/ 20
4	4.8	+ 2.65 -0.76 X 018	20/ 32	+ 2.83 -0.70 X 173	20/ 32
5	5.0	+ 2.50 -0.25 X 009	20/ 12	+ 3.00 -0.36 X 017	20/ 20
6	5.9	+ 2.61 -0.67 X 002	20/ 20	+ 1.68 -0.28 X 158	20/ 12
7	4.1	+ 1.66 -0.41 X 155	20/ 25	+ 1.69 -0.59 X 139	20/ 25
8	4.6	+ 0.62 -0.33 X 009	20/ 12	+ 0.49 -0.20 X 031	20/ 20
9	3.7	+ 0.02 -0.21 X 020	20/ 20	+ 0.13 -0.09 X 041	20/ 20
10	3.5	+ 2.32 -0.35 X 170	20/ 32	+ 2.04 -0.45 X 159	20/ 25
11	5.1	+ 0.75 -0.29 X 031	20/ 12	+ 1.08 -0.48 X 051	20/ 12
12	5.3	+ 0.21 -0.25 X 135	20/ 12	+ 0.69 -0.56 X 020	20/ 20
13	4.9	+ 2.19 -0.67 X 080	20/ 12	+ 2.33 -0.28 X 101	20/ 12
14	4.2	+ 1.77 -0.45 X 002	20/ 25	+ 1.89 -0.21 X 097	20/ 25
15	4.4	+ 4.70 -0.24 X 179	20/ 32	+ 4.32 -0.28 X 072	20/ 25
16	4.9	+ 0.91 -0.07 X 015	20/ 20	+ 1.19 -0.38 X 013	20/ 20
17	3.5	+ 3.91 -0.66 X 176	20/ 25	+ 4.87 -0.45 X 130	20/ 32
18	5.8	+ 0.62 -0.70 X 152	20/ 12	+ 1.16 -0.79 X 019	20/ 12
19	4.4	+ 2.12 -0.87 X 003	20/ 32	+ 2.03 -0.70 X 172	20/ 25
20	4.1	+ 1.76 -0.39 X 049	20/ 12	+ 2.15 -0.26 X 119	20/ 20
21	3.2	+ 1.91 -0.83 X 103	20/ 25	+ 0.99 -0.35 X 098	20/ 20
22	3.8	+ 2.27 -0.10 X 141	20/ 32	+ 2.93 -0.29 X 083	20/ 25
23	5.7	+ 1.62 -0.45 X 098	20/ 12	+ 1.71 -0.62 X 086	20/ 20
24	4.8	+ 1.01 -0.43 X 014	20/ 20	+ 1.19 -0.38 X 026	20/ 20
25	3.4	+ 1.54 -0.12 X 001	20/ 20	+ 1.78 -0.31 X 167	20/ 20
26	3.1	+ 1.53 -0.44 X 180	20/ 25	+ 1.58 -0.53 X 174	20/ 25
27	4.3	- 0.25 -0.25 X 100	20/ 25	+ 0.37 -0.62 X 095	20/ 25
28	4.3	+ 1.65 -0.23 X 156	20/ 12	+ 1.69 -0.09 X 163	20/ 12
29	4.3	+ 1.16 -0.04 X 154	20/ 12	+ 1.63 -0.35 X 105	20/ 12

TABLE B.2.2 Summary of participation for all subjects aged 3 to < 6 years.

Subject	Blur + Disparity 100cm	Blur + Disparity 33cm	Blur-only 100cm	Blur-only 33cm	Disparity-only 100cm	Disparity-only 33cm	Lenses 100cm	Prism 33cm	Blur Detection	DOF	Passive Condition	Active Condition
1	X	X	X	X	X	X	X	X	X		X	X
2									X		X	X
3	X	X	X	X	X	X		X	X		X	X
4	X	X	X	X	X	X		X			X	
5	X	X	X	X	X	X		X	X		X	X
6	X	X	X	X	X	X		X	X		X	X
7	X	X	X	X	X	X	X	X	X		X	
8	X	X	X	X	X	X	X	X	X		X	X
9	X	X	X	X	X	X	X	X				X
10	X	X	X	X	X	X	X	X			X	
11	X	X	X	X	X	X	X	X	X		X	X
12	X	X	X	X	X	X	X	X			X	X
13	X	X	X	X	X	X	X	X	X		X	X
14	X	X	X	X	X	X	X	X				X
15	X	X	X	X	X	X	X	X	X		X	X
16	X	X	X	X	X	X	X	X				
17	X	X	X	X	X	X	X	X	X		X	X
18	X	X	X	X	X	X	X	X	X		X	X
19	X	X	X	X	X	X	X	X	X		X	X
20	X	X	X	X	X	X	X	X	X		X	X
21	X	X	X	X	X	X	X	X				X
22	X	X	X	X	X	X	X	X	X		X	X
23	X	X	X	X	X	X	X	X	X		X	X
24	X	X	X	X	X	X	X	X	X		X	X
25	X	X	X	X	X	X	X	X			X	
26	X	X	X	X	X	X	X	X				
27	X	X	X	X	X	X	X	X	X		X	X
28	X	X	X	X	X	X	X	X	X		X	X
29	X	X	X	X	X	X	X	X			X	X

TABLE B.2.3 Summary of subjects' age, mean cycloplegic refractive error as obtained by the Grand Seiko autorefractor, and visual acuity for each eye in children ≥ 6 years of age. (Note: Visual acuity was tested using HOTV for children < 8 years and ETDRS in children ≥ 8 years; children with ETDRS VA are marked with an asterisk).

Subject	Age	OD Refractive Error	OD VA	OS Refractive Error	OS VA
30	8.8	+ 0.54 -0.57 X 090	20/ 20*	- 0.17 -0.15 X 162	20/ 25*
31	6.4	+ 1.47 -0.24 X 180	20/ 12	+ 1.55 -0.31 X 002	20/ 12
32	7.5	+ 1.17 -0.18 X 158	20/ 12	+ 1.48 -0.58 X 177	20/ 12
33	7.2	+ 0.86 -0.61 X 138	20/ 12	+ 0.66 -0.62 X 045	20/ 12
34	6.3	+ 5.32 -0.82 X 010	20/ 25	+ 4.78 -0.39 X 162	20/ 20
35	6.3	+ 0.58 -0.29 X 029	20/ 12	+ 0.75 -0.20 X 180	20/ 12
36	6.7	+ 1.11 -0.68 X 034	20/ 25	+ 0.83 -0.87 X 167	20/ 25
37	6.1	+ 0.25 -0.00 X 180	20/ 12	+ 0.16 -0.40 X 102	20/ 12
38	6.9	+ 1.13 -0.48 X 013	20/ 12	+ 0.82 -0.26 X 176	20/ 12
39	9.9	+ 0.16 -0.08 X 019	20/ 16*	+ 0.46 -0.37 X 002	20/ 16*
40	9.5	+ 1.08 -0.12 X 157	20/ 16*	+ 1.25 -0.04 X 006	20/ 12*
41	7.0	+ 1.76 -0.44 X 070	20/ 12	+ 1.98 -0.35 X 177	20/ 12
42	8.2	+ 1.21 -0.54 X 063	20/ 20*	+ 1.75 -0.41 X 174	20/ 12*
43	9.6	+ 0.81 -0.16 X 038	20/ 16*	+ 1.27 -0.50 X 129	20/ 16*
44	6.2	+ 1.83 -1.07 X 085	20/ 20	+ 1.78 -0.65 X 118	20/ 12
45	6.6	+ 1.91 -0.25 X 156	20/ 12	+ 2.12 -0.21 X 117	20/ 12
46	6.2	+ 1.58 -0.17 X 159	20/ 12	+ 1.20 -0.28 X 113	20/ 12
47	7.5	+ 1.12 -0.58 X 033	20/ 12	+ 0.79 -0.16 X 145	20/ 12
48	6.0	+ 1.60 -0.92 X 036	20/ 12	+ 1.44 -0.63 X 163	20/ 12
49	6.0	+ 1.08 -0.17 X 009	20/ 12	+ 1.24 -0.19 X 075	20/ 12
50	6.3	+ 2.44 -1.00 X 027	20/ 12	+ 1.80 -0.60 X 156	20/ 12
51	8.8	+ 2.02 -0.55 X 001	20/ 12*	+ 1.85 -0.20 X 066	20/ 12*
52	8.8	+ 1.90 -0.14 X 052	20/ 12*	+ 1.50 -0.30 X 012	20/ 16*
53	6.1	+ 2.45 -0.44 X 178	20/ 12	+ 2.27 -0.25 X 021	20/ 12
54	7.2	+ 5.16 -0.66 X 029	20/ 20	+ 4.53 -0.53 X 174	20/ 20
55	7.9	+ 1.08 -0.41 X 174	20/ 16	+ 1.22 -0.73 X 152	20/ 12
56	6.8	+ 0.46 -0.05 X 031	20/ 12	+ 0.73 -0.30 X 164	20/ 12
57	6.3	+ 2.30 -0.30 X 038	20/ 20	+ 2.33 -0.25 X 102	20/ 20
58	7.9	+ 0.41 -0.24 X 143	20/ 16	+ 0.45 -0.40 X 134	20/ 16
59	7.3	+ 0.92 -0.12 X 097	20/ 20	+ 1.20 -0.33 X 004	20/ 16

TABLE B.2.4 Summary of participation for all subjects aged ≥ 6 years.

Subject	Blur + Disparity 100cm	Blur + Disparity 33cm	Blur-only 100cm	Blur-only 33cm	Disparity-only 100cm	Disparity-only 33cm	Lenses 100cm	Prism 33cm	Blur Detection	DOF	Passive Condition	Active Condition
30	X	X	X	X	X	X		X	X		X	X
31	X	X	X	X	X	X		X	X		X	X
32	X	X	X	X	X	X	X		X		X	X
33	X	X	X	X	X	X		X	X		X	X
34	X	X	X	X	X	X	X	X	X		X	X
35	X	X	X	X	X	X	X	X	X		X	X
36	X	X	X	X	X	X	X	X	X	X	X	X
37	X	X	X	X	X		X	X	X	X	X	X
38	X	X	X	X	X	X	X	X	X		X	X
39	X	X	X	X	X	X	X	X	X	X	X	X
40	X	X	X	X	X	X	X	X	X	X	X	X
41	X	X	X	X	X	X		X	X	X	X	X
42	X	X	X	X	X	X	X	X	X	X	X	X
43	X	X	X	X	X	X	X	X	X	X	X	X
44	X	X	X	X	X	X	X	X	X	X	X	X
45	X	X	X	X	X	X	X	X	X	X	X	X
46	X	X	X	X	X	X	X	X	X		X	X
47	X	X	X	X	X	X	X	X	X	X	X	X
48	X	X	X	X	X	X	X	X	X		X	X
49	X	X	X	X	X	X	X	X	X		X	X
50	X	X	X	X	X	X	X	X	X		X	X
51	X	X	X	X	X	X	X	X	X	X	X	X
52	X	X	X	X	X	X	X	X	X	X	X	X
53	X	X	X	X	X	X	X	X	X		X	X
54	X	X	X	X	X	X	X	X	X		X	X
55	X	X	X	X	X	X	X	X	X		X	X
56	X	X	X	X	X	X	X	X	X		X	X
57	X	X	X	X	X	X	X	X	X		X	X
58	X	X	X	X	X	X	X	X	X	X	X	X
59	X	X	X	X	X	X	X	X	X		X	X

TABLE B.2.5 Summary of subjects' age, mean cycloplegic refractive error as obtained by the Grand Seiko autorefractor, and visual acuity for each eye as measured by ETDRS in the adult subjects who participated in the experiments.

Subject	Age	OD Refractive Error	OD VA	OS Refractive Error	OS VA
63	24.0	+ 0.86 -0.49 X 135	20/ 16	+ 1.04 -0.58 X 028	20/ 16
64	23.3	+ 1.00 -0.46 X 175	20/ 16	+ 1.79 -0.53 X 167	20/ 16
65	24.1	+ 0.37 -0.40 X 151	20/ 16	- 0.01 -0.22 X 007	20/ 16
66	25.3	+ 0.70 -0.23 X 047	20/ 16	+ 0.87 -0.33 X 126	20/ 12
67	23.9	+ 1.25 -0.25 X 112	20/ 16	+ 1.37 -0.16 X 039	20/ 16
68	23.6	+ 0.65 -0.39 X 167	20/ 12	+ 0.87 -0.04 X 125	20/ 12
69	25.3	+ 0.60 -0.30 X 098	20/ 16	+ 1.00 -0.29 X 179	20/ 12
70	25.0	+ 0.87 -0.16 X 116	20/ 16	+ 0.50 -0.66 X 096	20/ 25
71	31.6	+ 0.75 -0.00 X 000	20/ 16	+ 0.83 -0.04 X 088	20/ 12
72	26.8	+ 1.29 -0.37 X 054	20/ 16	+ 1.12 -0.33 X 052	20/ 16

TABLE B.2.6 Summary of participation for all adult subjects who participated in the experiments.

Subject	Blur + Disparity 100cm	Blur + Disparity 33cm	Blur-only 100cm	Blur-only 33cm	Disparity-only 100cm	Disparity-only 33cm	Lenses 100cm	Prism 33cm	Blur Detection	DOF	Passive Condition	Active Condition
63	X	X	X	X	X	X	X	X	X	X	X	X
64	X	X	X	X	X	X	X	X	X	X	X	X
65	X	X	X	X	X	X	X	X	X	X	X	X
66	X	X	X	X	X	X	X	X	X	X		
67	X	X	X	X	X	X	X	X	X	X	X	X
68	X	X	X	X	X	X	X	X	X	X	X	X
69	X	X	X	X	X	X	X	X	X	X	X	X
70	X	X	X	X	X	X	X	X	X	X		
71	X	X	X	X	X	X	X	X	X	X	X	X
72	X	X	X	X	X	X	X		X	X	X	X

Appendix C. Experimental Set-up

FIGURE C.1.1 Image of experimental setup. The red rectangle indicates the location of the beam splitter.

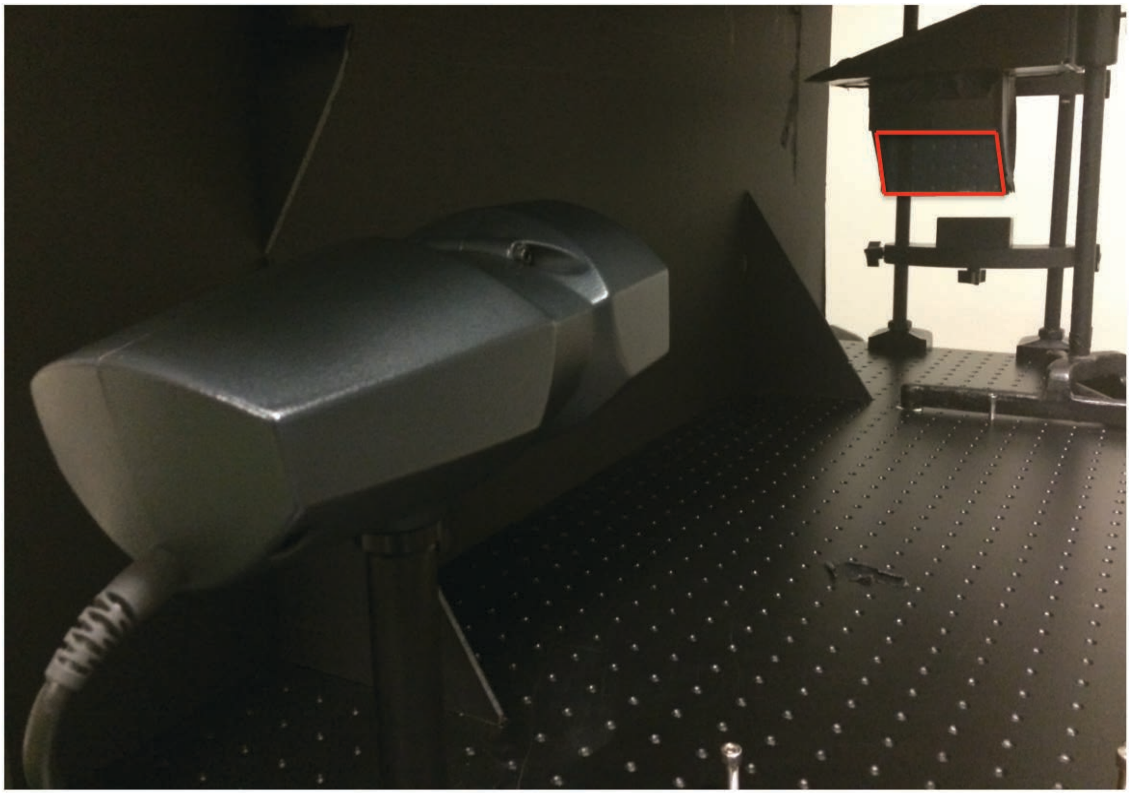
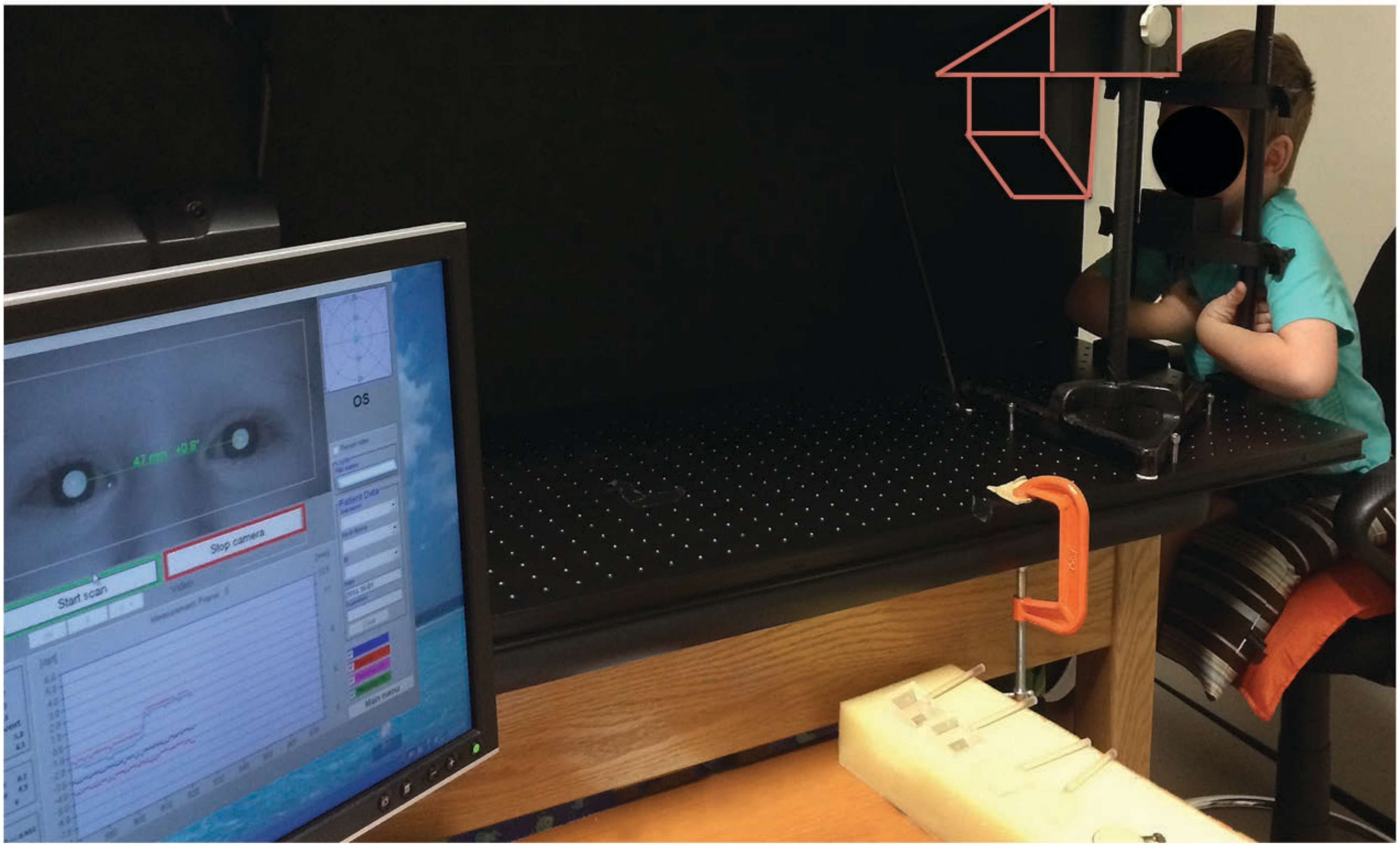


FIGURE C.1.2 Image of experimental setup with subject in place.



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