CHARACTERISTICS OF ACCOMMODATIVE BEHAVIOR DURING SUSTAINED PERIODS OF NEAR WORK IN HUMANS AND PRIMATES

A thesis presented to the graduate faculty of
The New England College of Optometry in partial fulfillment
of the requirements for the degree of Master of Science

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PURPOSE

The role of accommodation in the development of a refractive state remains unclear. Studies in animals and humans have suggested that a relationship, if one exists, may involve inaccuracies in accommodation during nearwork. Additionally, studies of accommodation typically look at the response over brief periods of time under controlled visual environments. We studied various dynamic characteristics of accommodative behavior during sustained periods of reading in human emmetropes and myopes and during an operant conditioned near visual matching task in rhesus macaques in order to define any relationships between accommodative behavior and the development of myopia.

METHODS

Humans: Accommodation was binocularly measured with an infrared photorefractor (PowerRefractor) in twenty young adults with stable refractive errors ranging from +0.50D to -7.0D during sustained reading at several distances (1.5D, 2.5D, and 3.5D). All subjects were measured with pupil dilation (2.5% phenylepherine) and full correction. Accommodative response, errors, and accommodative variability, including power spectrum analysis, were

analyzed over the entire reading period. Relationships between accommodative characteristics and changes in accommodative demand and refractive error were determined. *Non-human:* Three adult rhesus macaques were trained to perform a visual match–to–sample task that required the monkey to look at a video display while manipulating a cursor with a joy-stick to indicate a response. The monkeys were trained to look at the monitor binocularly through a mask integrated into the testing cage so that while performing the task their accommodative behavior could be measured using an infrared video photorefractor. Refractions and eye position were recorded throughout several testing sessions at several working distances (20–60 cm).

RESULTS

Humans: All accommodative behaviors showed large inter-subject variability at all of the reading demands. Accommodative lags significantly increased with closer demands (Mean lag (D): 0.689D at 1.5D, 0.877D at 2.5D, 0.987D at 3.5D (ANOVA:$p<0.05$), yet no relationship was found between myopia and accommodative errors. Accommodative variability significantly increased with closer demands (Mean standard deviation (D) (±s.e.): 0.151D (0.017) at 1.5D, 0.198D (0.017) at 2.5D, 0.299D (0.146) at 3.5D (ANOVA: $p<0.01$)) and with increasing myopia (ANOVA: $p<0.05$). Power spectrum analysis showed a significant increase in the power of accommodative microfluctuations with closer demands (ANOVA: $p<0.05$) and in myopes at the closest reading demand (ANOVA: $p<0.01$). *Non-human:* Refractions measured while the monkeys were actively on task indicate that the accommodative response was variable, but on average responsive to the stimulus demands.

The standard deviations of the mean accommodative responses ranged from ±0.5 to ±2.2 D, and were significantly greater at the closer working distances (ANOVA, $p<0.05$). Accommodation stimulus–response functions show that, on average, the monkeys accommodate to the monitor at all working distances tested (average slope = 0.989 ±0.162). The mean accommodative lag was 0.78 ±0.41 D. Examination of the distribution of refractions shows both normal and bi-modal distributions. The bi-modal distributions are peaked near the stimulus demand and the subject's distance refraction.

CONCLUSIONS

Accommodation in humans and rhesus macaques is variable during sustained periods of near work under free viewing conditions. Differences in accommodative behaviors at different accommodative demands and their relationship to stable refractive error in humans suggest a possible role for the development of myopia. Emmetropic children with previously identified risk factors as well as those with progressing myopia need to be studied to determine if such accommodative characteristics are risk factors for the development and/or progression of myopia in humans. Further study of the accommodative behavior in rhesus macaques is needed to make definitive conclusions about differences in the accuracy of accommodation with varying task demands and it’s possible role in the development of refractive state.

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GENERAL OVERVIEW

A correlation between myopia and education (e.g. Al-Bdour, Odat & Tahat, 2001; Au Eong, Tay & Lim, 1993; Goldschmidt, 1962; Hepsen, Evereklioglu & Bayramlar, 2001; Richler & Bear, 1980; Sperduto, Seigel, Roberts & Rowland, 1983; Young, Leary, Baldwin, West, Box, Harris & Johnson, 1969) has led to speculation that the amount of reading a child does may be a risk factor for the development of myopia, although several studies have reported contradictory results (Mutti, Mitchell, Moeschberger, Jones & Zadnik, 2002; Saw, Nieto, Katz, Schein, Levy & Chew, 2000; Wu, Seet, Yap, Saw, Lim & Chia, 2001; Zadnik, 1997). Additional research has suggested that accommodation is the link between near work and myopia (reviewed by Rosenfield, 1998 and Rosenfield & Gilmartin, 1998), but there is little direct evidence for or against this assertion. Thus, the question of how accommodation during near work might relate to the development of myopia remains largely unanswered. Several aspects of accommodation have been suggested as possible risk factors; decreased accommodative tonus (McBrien & Millodot, 1987; Rosenfield & Gilmartin, 1987), decreased accommodative amplitude (McBrien & Millodot, 1986), increased accommodative lags (Abbott, Schmid & Strang, 1998; Goss, 1988; Gwiazda, Thorn, Bauer & Held, 1993; Gwiazda, Thorn & Held, 2005; Nakatsuka, Hasebe, Nonaka & Ohtsuki, 2005), increased accommodative adaptation (Chen, Schmid, Brown & Edwards, 2005; Gilmartin & Bullimore, 1991; Gwiazda, Bauer, Thorn & Held, 1995b; McBrien & Millodot, 1988; Strang, Winn & Gilmartin, 1994), and increased accommodative fluctuations (Harb, Thorn & Troilo, 2003; Seidel, Gray & Heron, 2003) have all been found in myopes, although it is unclear how such risk factors might induce myopia.

One hypothesis is that hyperopic retinal defocus resulting from a large accommodative lag during periods of extended nearwork might result in compensatory axial elongation of the eye and ultimately myopia (Abbott et al., 1998; Gwiazda, Bauer, Thorn & Held, 1995a; Gwiazda et al., 1993; Gwiazda et al., 2005; Nakatsuka et al., 2005). Animal studies have shown that imposing hyperopic defocus with negative lenses induces a compensatory increase in eye growth and myopia (Graham & Judge, 1999; Hung, Crawford & Smith, 1995; Schaeffel, Glasser & Howland, 1988; Whatham & Judge, 2001) and a compensatory axial hyperopia in response to positive lenses (Schaeffel et al., 1988; Smith III, Hung & Harwerth, 1994; Whatham & Judge, 2001), supporting the existence of visually guided eye growth control (for a recent review see Wallman and Winawer (2004)).

How accommodation is related to visually guided eye growth is unclear, but important to determine because accommodation, like defocusing lenses, changes the retinal image quality. The possible role of accommodation in the control of eye growth has been questioned by studies that have shown intact eye growth mechanisms despite the blocking of ciliary muscle activity through several different experimental mechanisms; pharmacological blocking of accommodation (Schaeffel & Diether, 1999; Schwahn & Schaeffel, 1994), severing of the ciliary muscle (Wildsoet, Howland, Falconer & Dick, 1993), or lesion of the Edinger-Westphal nucleus controlling accommodation (Schaeffel, Troilo, Wallman & Howland, 1990). Therefore, understanding how accommodative behavior and the ability to focus on the plane of regard while performing sustained near tasks may be useful in understanding any relationship between accommodation, near work, and the development of myopia.

Studies of accommodation in humans are typically performed during brief near tasks under tightly controlled environments in order to understand the stimuli driving accommodation and the dynamics of the accommodative response (e.g. Abbott et al., 1998; Gwiazda et al., 1993; Gwiazda et al., 2005; McBrien & Millodot, 1986; Nakatsuka et al., 2005). Very little is known about accommodative behavior during sustained periods of near work in natural visual environments in humans or primates. The aim of this study is to identify and describe several aspects of accommodative behavior over sustained periods of near-work in a close-to-natural setting in humans and primates.

More specifically, these human studies explore the dynamics of accommodative inaccuracies, during sustained near reading, both in terms of response errors (lag or lead of accommodation) and accommodative variability, and whether there are differences in emmetropes and myopes. The results of studies within these two areas will be discussed in separate chapters that specifically look at how differences in accommodative demand, subject refractive error, or duration of reading are related to these accommodative behaviors. Although we cannot say whether the accommodative behaviors observed in this study are the cause or effect of refractive error development, they will help provide information about the dynamic characteristics of visual blur during sustained periods of reading and can be used in further studies.

In the final chapter, the observation and description of accommodation behaviors in rhesus macaques while performing a near point operant conditioned match-to-sample task over sustained periods of time will be discussed. This study examines the dynamics of accommodation in a similar way to the human descriptions in order to describe the accuracy

of the accommodative system in macaques during near free-viewing and if any relationships exist with changes in accommodative demand or accuracy of matching task. Although this study is purely preliminary, the examination of accommodation in primates during a sustained near task in free space is typically not described and proves insightful in the possibility of future studies to define possible relationships between accommodative behaviors and the development of myopia.

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CHAPTER 1

ACCOMMODATIVE RESPONSE ERRORS DURING SUSTAINED READING

INTRODUCTION

Errors in accommodation are most commonly described as a lag (insufficient accommodation where a subject's focus is further than the target) or a lead (excess of accommodation causing the subjects' focus to be closer than the target). A lag of accommodation produces a hyperopic defocus relative to the target (image focused behind the retina) and an accommodative lead produces a myopic defocus relative to the target (image focused in front of the retina). Accommodative errors, specifically lags of accommodation, have frequently been described in human subjects while reading and at times can be substantial (Harb, Thorn & Troilo, 2003; Schaeffel, Weiss & Seidel, 1999; Seidemann & Schaeffel, 2003).

Since the hyperopic defocus from negative lens wear produces axial elongation of the eye and an accommodative lag produces a similar, but smaller, hyperopic defocus, a relationship between accommodation and eye growth control may exist. Boisvert & Troilo (2000) and Baker & Troilo (2002) explored this question by measuring accommodative stimulus-response functions in a marmoset primate model. Baker and Troilo described that lags of accommodation were generally higher (accommodative-stimulus response gain lower) after axial myopia was induced suggesting that an altered accommodative function followed the experimental manipulation of eye growth. Baker and Troilo report no statistically significant relationship between accommodative gain before the experimental

manipulation and the amount of axial growth induced by negative lens wear, further supporting the view that changes in accommodative gain associated with myopia are an effect, rather than a cause of the myopia.

Human studies have shown that progressing myopic children have greater accommodative lags compared to emmetropes (Drobe & de Saint-Andre, 1995; Goss, 1991; Gwiazda, Thorn, Bauer & Held, 1993; Gwiazda, Thorn & Held, 2005; Nakatsuka, Hasebe, Nonaka & Ohtsuki, 2005) and stable myopes (Gwiazda, Bauer, Thorn & Held, 1995). Gwiazda et al. (1995) described refractive changes in myopic children to accommodative response functions over a 12-month period. In general, progressing myopes had shallower accommodative stimulus-response functions (reduced gain) as compared to stable myopes. This increased accommodative lag has been described to manifest as much as 2 years prior to onset of myopia and therefore may be a precursor to the progression of myopia (Gwiazda et al., 2005). Abbott et al. (1998) further explored the effect of myopia progression on the stability of the accommodative response by separating an adult myopic population into progressing and stable, regardless of onset. Similar to the finding by Baker & Troilo (2002), the rate of progression of myopia did not statistically correlate with the accommodative stimulus-response slope (gain) (Abbott, Schmid & Strang, 1998). While many other studies have reported an accommodative lag in myopes, the range in lags reported are substantial as can be seen in Tables 1 and 2. While these studies provide insight into the role of accommodation on the development of myopia, they all describe the accommodative response during brief periods of time in a controlled environment.

Table 1
Mean lags of accommodation as reported by various studies.

Study	Subject Age	Mean Lag (D)
Chen & O'Leary (2000)	2-5	0.24D (distance induced); 0.69D (lens induced)
Gwiazda et al. (1993)	5-17	0.78D at 3D demand (distance induced); 2.8D at 3.5D demand (lens induced)
Jackson & Goss (1991)	8-16	0.23D (school-aged children with 40cm working distance using MEM retinoscopy)
McBrien & Millodot (1986b)	18-23	0.40D at 3D demand
Rouse et al. (1984)	4-12	0.34D (school-aged children with habitual working distance using MEM retinoscopy)
Schaeffel et al. (1999)	25-35	0.30 D (myopes and emmetropes at 3.5D demand)
Seidemann & Schaeffel (2003)	20-38	0.35D(3D demand); 0.48D(4D demand); 0.60D(5D demand)

Table 2
Mean difference in accommodative response (lag) between myopic and emmetropic populations (mean difference in lag= myopes – emmetropes).

Study	Subject Age	Demand (D)	Mean Difference (D)
Bullimore et al. (1992)	19-23	3	0 D (active condition)[a] 0.08 D (passive condition)[b]
Gwiazda et al. (1993)	5-17	3	0 D (positive lens series while viewing a 25cm target) 0.20 D (decreasing distance series) 0.90 D (negative lens series while viewing a 4m target)
McBrien & Millodot (1986b)	18-23	3	0.16 D (late onset myope)
Rosenfield & Gilmartin (1988)	19-24	3	0.22 D
Rosenfield et al. (2002)	21-27	4	0.11 D

[a] – active condition of adding numbers [b]- passive condition of reading numbers

The use of plus lenses (bifocals and progressive addition lenses) during reading has been proposed as a possible treatment regime for myopia progression for many years. The hypothesis of plus lenses as a treatment for myopia is that by effectively reducing the hyperopic defocus caused by an abnormally large accommodative lag, the stimulus for eye elongation is minimized, although this hypothesis has been contradicted by studies that have described non-accommodative mechanisms of eye growth control (Bartmann & Schaeffel, 1994; McBrien, Moghaddam & Reeder, 1993; Schaeffel, Troilo, Wallman & Howland, 1990). Goss (1986) described the effect of bifocal lenses on the progression of myopia in 1985 and stated that myopic progression was reduced (by 0.07D) in the bifocal group, yet was not significant (Goss, 1986). A double-blind nationwide longitudinal study, C.O.M.E.T., in which myopic children received progressive plus lenses, found that children prescribed progressive plus lenses had on average 0.20 D less myopia then when compared to the single-vision minus lens group at one year, which was maintained at the same level over then next two years (Gwiazda, Hyman, Hussein, Everett, Norton, Kurtz, Leske, Manny, Marsh-Tootle, Scheiman & Group, 2003). When the data was sub-grouped, they found that children with accommodative lags > 0.43D and a near-point esophoria had a more clinically significant treatment effect of 0.64 D over the 3 year treatment period (Gwiazda, Hyman, Norton & al., 2004). Children with near-point esophoria tend to accommodate less during near tasks (Goss, 1991; Gwiazda, Grice & Thorn, 1999; Nakatsuka et al., 2005) in order to maintain ocular alignment, thereby increasing their accommodative lag. Fulk & Cyert (1996) measured the rate of myopia progression in myopic children with near-point esophoria and found a decreased rate (0.30D / year less) in the bifocal group (Fulk & Cyert, 1996). Overall,

bifocal studies have not been consistently effective in reducing myopia progression in all individuals, further leading to the complexity of the relationship between accommodation and myopia progression.

The aim of this study is to describe the dynamic characteristics of accommodative errors, in terms of lags or leads and accommodative stimulus-response functions during sustained periods of near reading in a close-to-natural visual environment in myopes and emmetropes at several reading distances to determine if any relationships exist.

METHODS

Subjects

Accommodation during reading was examined in 20 subjects (optometry students aged 22-28), with normal binocular vision and with stable refractive errors ranging from +0.50D to -7.0D (11 myopes and 9 emmetropes (±0.50D)). Stability of refractive error was self-reported by the subjects and defined as a change of ±0.50D or less in the last two years. Myopic subjects were fully corrected with their habitual contact lens corrections. The pupils of all subjects were dilated with 2 drops of 2.5% phenylepherine 45 minutes prior to measurements to prevent significant changes in pupil size. Although this is not considered a natural state in which we read, subject's pupils were dilated to reduce fluctuations in pupil size, which could affect the performance of the optometer. The PowerRefractor has been shown to have no systematic change in refraction measures with varying pupil sizes (Choi et al., 2000) within a narrow range of relatively large pupil sizes (approximately 4mm to 7mm), but the accommodative demands in our set-up often resulted in pupil constriction outside of

this reliable range. While in some studies phenylephrine has been shown to have an insignificant effect on the accommodative response and dynamics (Ciuffreda, 1998; Ostrin & Glasser, 2004), others have described a small decrease (<11%) in subjects' amplitude of accommodation (Culhane, Winn & Gilmartin, 1999; Gimpel, Doughty & Lyle, 1994). If present, such a small decrease in the amplitude of accommodation in young subjects with large amplitudes of accommodation (Hofstetter's minimum amplitude= 9.5D for a 22 year old, (Hofstetter, Griffin, Berman & Everson, 2000)) would not affect accommodative responses at normal reading distances. All research performed in this study adhered to the tenets of the Declaration of Helsinki and was approved by the Institutional Review Board of The New England College of Optometry.

Reading Task

Subjects read an excerpt from "The Call of the Wild" (black letters on a white background- Times New Roman font) displayed on a computer monitor at three different distances (66.6cm, 40cm, and 28.6cm) corresponding to accommodative demands of 1.5D, 2.5D, and 3.5D. The accommodative response to printed text has been shown to be no different than to a visual display terminal [Sorkin, 2003 #885], therefore a computer monitor was used to allow for greater control of gaze position. A text window, with a conserved angular subtense of 9.5º horizontal x 4.5° vertical was used on the VDT. Letter height was maintained at 0.36° for all distances as well. The average luminance of the VDT was 14.3 c/m^2. Subjects were instructed to read silently for 10 minutes and were able to control their own reading pace by scrolling through the text window. Subjects were instructed to read as

they would normally and were allowed to look away from the text at their discretion (while maintaining their head in a chin-rest). The frequency of fixation breaks and the corresponding accommodative response data were recorded. Although the subjects were not tested for reading speed or comprehension of the reading material, they presumably were reading as appropriate saccadic eye movements were observed by the examiner (EH). Reading tasks at all 3 near working distances were performed in a random order within a single day.

Measurement of Accommodation and Eye Position

Refractive state (in the vertical meridian), pupil diameter, and eye position were measured binocularly (one eye used for accommodation analysis) at a rate of 25 Hz using an eccentric infrared photorefractor (PowerRefractor - MultiChannel Systems; Reutlingen, Germany). The refractor was positioned 1M away from the subject and 5º-8º above the top of the text window, and was directed between the subject's eyes. The camera's infrared light source has been established for safe use with adults and children (Choi, Weiss, Schaeffel, Seidmann, Howland, Wilhelm & Wilhelm, 2000).

Calibration of the PowerRefractor

The PowerRefractor was calibrated in a separate group of 21 subjects (21-28 years of age) with normal binocular vision and with refractive errors (spherical equivalents) ranging from +1.00D to -5.00D.The range of refractive errors used for calibration was within the limits of the instrument (±5D) as described by Choi et al. (2000). Subjects were cyclopleged

with 2 drops of 1.0% cyclopentolate 45 minutes prior to calibration measurements to control for pupil size and accommodation. Some subjects were measured both while uncorrected and while wearing their habitual contact lens corrections (on separate occasions) in order to increase the range of refractions measured (n=33 right eyes (12 subjects were measured under both conditions)).

After cycloplegia, retinoscopy was performed by an experienced examiner (FT) and subjective refraction measures, performed by another experienced examiner (EH), were also performed and showed a significant correlation (subjective refraction= -0.153 + 0.982(retinsocopy), R=0.94, correlation $p<0.01$). In the same subjects, PowerRefractor measures were made in the vertical meridian while the subject looked at a distant target (high contrast 20/100 Snellen E presented at 7.5M) for 15-20 seconds. To directly compare the PowerRefractor measures to the retinoscopy measures, the refractive power of the vertical meridian was calculated from the overall sphero-cylindrical retinoscopy measures ($J_{90}=J_{sph}\sin^2(\theta_{cyl}-90^o)$).

The PowerRefractor's infrared light source illuminates the fundus and the brightness of the reflex (pixel intensity slope) across the vertical meridian of the pupil is converted into refractive state using a built-in calibration function (Seidemann, Schaeffel, Guirao, Lopez-Gil & Artal, 2002). This function was found to over-estimate the levels of myopia and hyperopia when compared to our cycloplegic retinoscopy (Figure 1.1). Using the cycloplegic retinsocopy measures as a standard, a new calibration function was determined by converting PowerRefractor measures back into pixel intensity slopes and then re-converted to refractions (refraction = -0.883 + 1.5259(pixel intensity slope)). This new calibration function

correlated well with cycloplegic retinsocopy (Figure 1.2) and was applied to all subjects' accommodative measures prior to analysis.

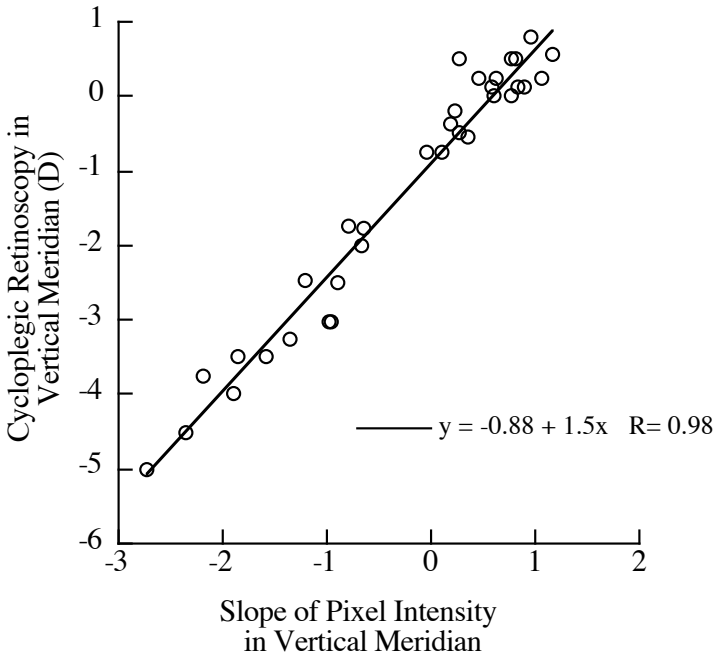


Figure 1.1 A new calibration function (linear regression function) was derived by comparing the slope of the pixel intensities across the vertical meridian of the pupil to cycloplegic retinoscopy across the same vertical meridian.

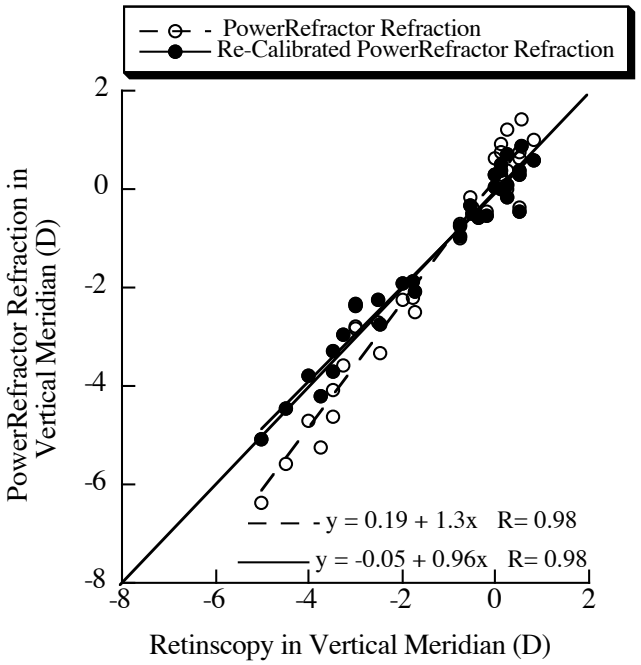


Figure 1.2 Prior to re-calibration (dashed line) the PowerRefractor over estimated the levels of myopia and hyperopia. After the new calibration function was applied (solid line) the PowerRefractor measures correlated well with retinoscopy at all refractive levels.

Filtration of the Accommodative Response

The accommodative response for each subject at each reading distance was measured continuously for 10 minutes. The response was filtered offline to remove measurement artifacts due to blinks and fixation breaks outside of the text window. In order to remove the artifacts associated with blinks without erroneously removing any true blur-driven accommodation, refractive changes that were too fast to be considered physiological (> 10 D/second) (Adrian Glasser, personal communication; Ciuffreda & Kruger, 1988) were filtered. These data were removed from the accommodative response by searching for differences greater than 10D/sec between two data points and then removing the point that was further away from the mean accommodative response. This technique effectively removed the artifactual peaks that were due to blinks. Figure 1.3 shows a 60-s clip of

accommodation before and after filtering for an individual. Even after filtering the accommodative response for blinks and fixation breaks, an appreciable amount of variability was still present, which will be discussed in Chapter 2.

Analysis of the Accommodative Response

The accommodative response was analyzed offline in a number of ways to determine if any significant relationships between the accommodative response metrics measured and reading behaviors might exist. The mean error in the accommodative response relative to the target demand (i.e. lead or lag) was determined for each subject in 10 one-minute periods for each reading distance. Individual stimulus-response functions were calculated using the three accommodative demands.

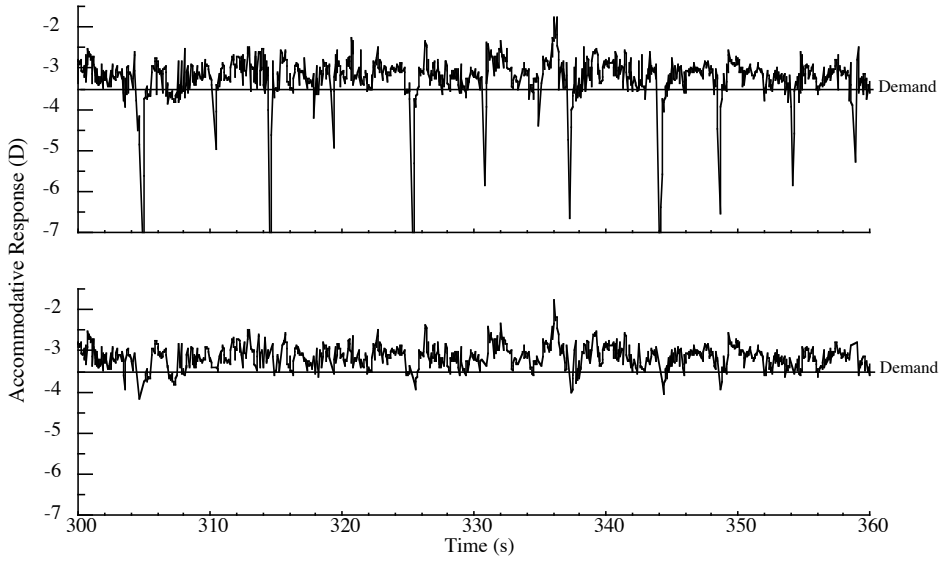


Figure 1.3 (A) The accommodative response (measured by the PowerRefractor) during one minute of the reading task (horizontal line indicates the accommodative demand). The large myopic deflections are artifacts due to blinks. **(B)** The filtered accommodative response after data corresponding to blinks and gaze breaks outside of the text window were removed.

Statistical Analysis

Repeated measures ANOVA models were used to determine if the accommodative measures changed over time or with different reading demands. Additionally, linear regression analysis was used to determine whether relationships existed between any of the accommodative measures and subject refractive state. Unpaired t-tests were used to compare accommodative measures between the myopic and emmetropic groups. Statistical analysis and curve fitting was performed using Statview (Abacus Concepts, Inc., Berkeley, CA.), and signal filtering and graphical analysis was performed using Kaleidagraph (Synergy Software, Reading, PA.)

RESULTS

As expected, the average accommodative error (measured as the difference between mean accommodative response and the target demand (- = lead, += lag)) observed was an accommodative lag at each of the reading distances (mean ranges of accommodative errors including all subjects: -0.36D to 1.31D at 1.5D demand; -0.31D to 1.78D at 2.5D demand; -0.06D to 1.71D at 3.5D demand). One individual demonstrated a substantial lead of accommodation at the 1.5D and 2.5D reading demands. This subject was, subsequent to our study, diagnosed with accommodative excess and was not included in the group analysis because of a failure to meet subject inclusion criteria of normal binocular vision. There was substantial inter-subject variability at all of the working distances, as illustrated in Figure 1.4. On average, the accommodative errors were greatest during the first 2-3 minutes of reading and then remained stable within subjects throughout the 10-minute reading period at all

distances tested (Figure 1.5). The mean lag of accommodation for the group significantly increased with closer reading distances as seen in Figure 1.4 (mean±s.e.: 0.69±0.08 D at 1.5D demand, 0.88±0.10 D at 2.5D demand, and 0.99±0.14 D at 3.5D demand; Repeated measures ANOVA: $p<0.05$)).

In general, the lag of accommodation was not significantly correlated with the subjects' refractive state (Figure 1.6; $R^2= 0.05$; $p=0.39$ at 2.5D, $R^2= 0.02$; $p=0.59$ at 3.5D), although at the 1.5 D demand the lag of accommodation tended to be greater in myopes ($R^2= 0.17$; $p=0.08$) and the mean lag of all myopes was greater than for emmetropes (mean±s.d: myopes, 0.84±0.27 D vs. emmetropes, 0.56±0.28 D; unpaired t-test, $p<0.05$).

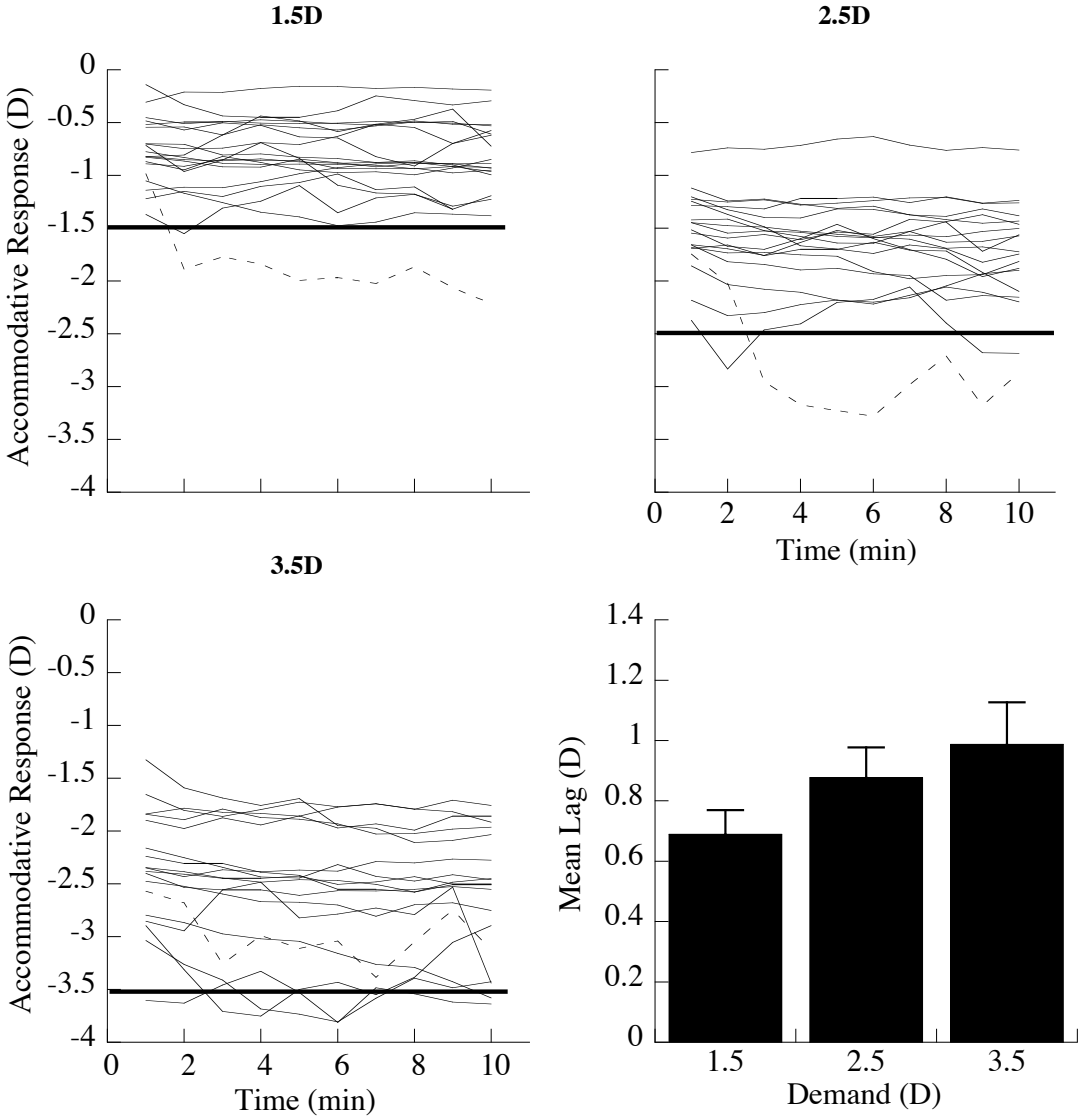


Figure 1.4 The average accommodative response during the reading period differed substantially between subjects at the three accommodative demands. Individual accommodative responses are shown as thin black lines. The dashed line indicates a subject who demonstrated a lead of accommodation and was diagnosed with an accommodative excess. The horizontal line denotes the accommodative demand at each reading distance. **(D)** The mean lag of accommodation ((mean±s.e.: 0.69±0.08 D at 1.5D demand, 0.88±0.10 D at 2.5D demand, and 0.99±0.14 D at 3.5D demand, ANOVA $p<0.01$) for the group at each reading distance.

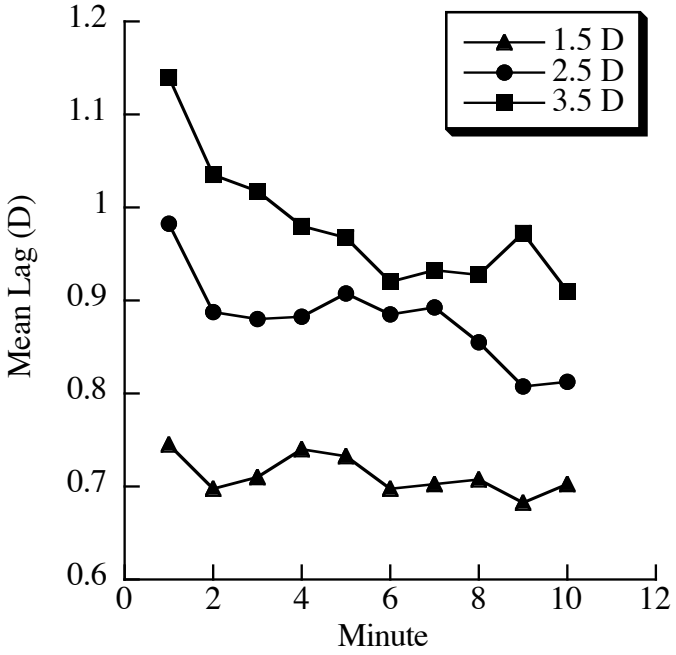


Figure 1.5 On average the mean lag of accommodation was largest in the first few minutes of reading and then decreased and remained stable for the remainder of the reading period at all of the reading distances (note: error bars were omitted for clarity).

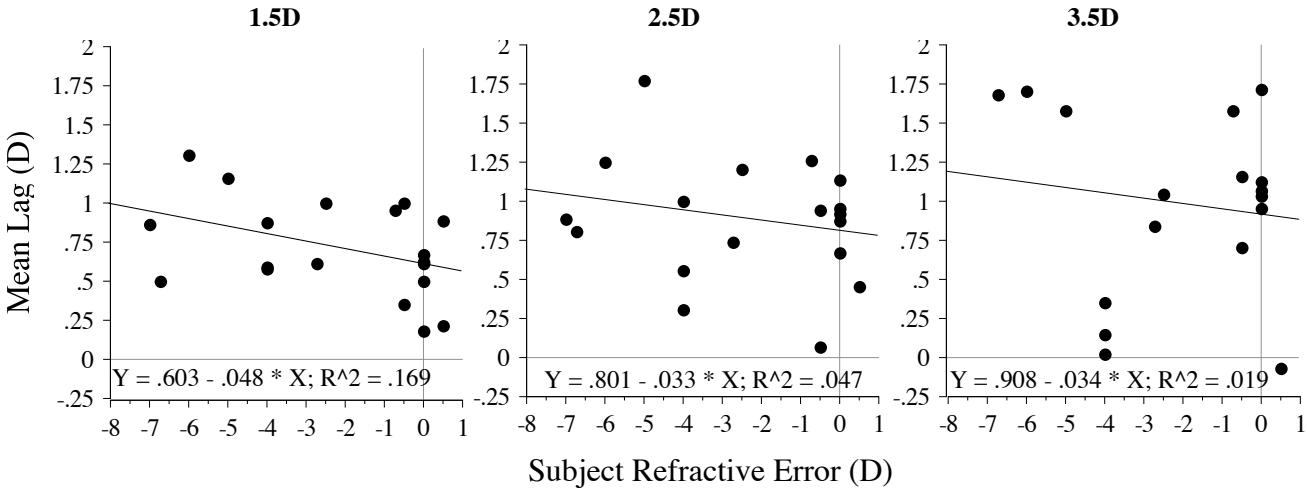


Figure 1.6 Linear regression analysis demonstrating the relationship between stable subject refractive error and mean lag of accommodative at each of the reading demands.

The accommodative stimulus-response function is another way to consider the lag of accommodation and how it changes with changing stimulus demands. We calculated the slopes of the stimulus-response functions for each individual based on the mean accommodative response at each of the three reading demands. There was substantial inter-subject variability in the slopes of the accommodative stimulus response function (Figure 1.7- Range: 0.41 to 1.36) yet, linear regression analysis demonstrated that there were no significant relationships with subject refractive error at any of the working distances (R^2 =0.015; p=0.64).

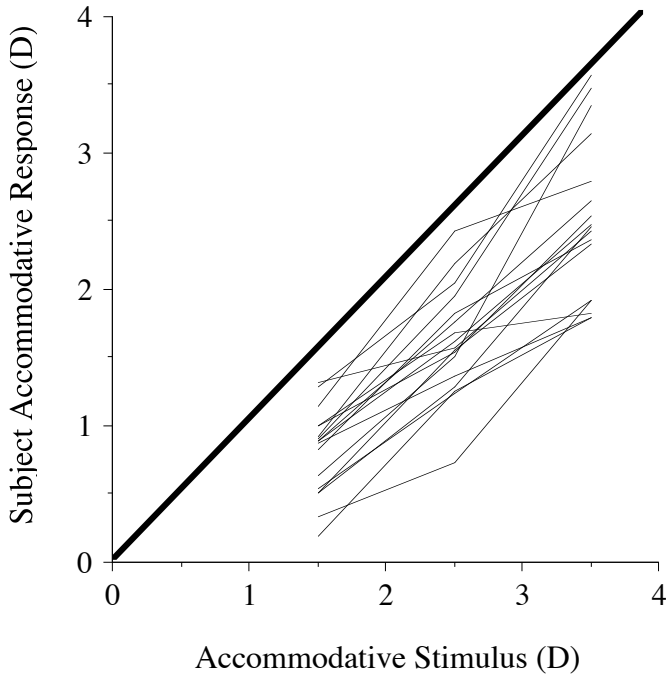


Figure 1.7 Individual accommodative stimulus response functions showing substantial inter-subject differences.

DISCUSSION

Often compared to the focusing system of a camera, accommodation has the primary function of reducing hyperopic retinal defocus during near work. Like a camera, accommodation is typically described in the literature as a 'snapshot' response to brief near tasks in controlled environments. This study examined the accommodative response over sustained periods of near reading in a more natural environment, to determine if accommodative response errors might have a relationship to the development of myopia.

In this chapter, several aspects of accommodative behavior that may be risk factors for myopia development were examined. The mean accommodative state during extended periods of reading was similar to that shown in other studies in which brief periods of accommodation to a fixed target were described (Gwiazda et al., 1993; McBrien & Millodot, 1986a; Nakatsuka, Hasebe, Nonaka & Ohtsuki, 2003; Nakatsuka et al., 2005). Although in the present study there were large differences in accommodative lags between subjects, individuals' lags were not correlated with refractive error. Overall, the average state of accommodation remains fairly stable over a 10-minute period within subjects, but there was some evidence of a slight trend toward an increased accommodative response after the first minute or two at the closer reading distances. A partial "correction" in the lag of accommodation within the first few minutes of reading has been previously described and is hypothesized to result from the increased output of the slow blur-driven accommodative response (SBAR) mediated by the sympathetic nervous system (Rosenfield & Gilmartin, 1998; Rosenfield & Gilmartin, 1999; Schor, Kotulak & Tsuetaki, 1986). Such an adaptation may increase the accuracy of the accommodative response during a sustained reading period

and ultimately increase subjective clarity. (Vera-Diaz, Gwiazda, Thorn & Held, 2004) also reported an increase in accommodative gain initially following viewing of a blurred image, although this adaptation was hypothesized to be a result of differences in the use of sensory blur cues between refractive error groups.

The lag of accommodation, on average, increased significantly with closer reading distances, which is consistent with earlier reports (Charman, 1999; Gwiazda et al., 1993; Seidemann & Schaeffel, 2003). Interestingly, some of the subjects in our study showed particularly large lags of accommodation (>1.0 D), but this did not seem to compromise their ability to read, raising questions about how the subjects were able to read through substantial hyperopic defocus. However, some of the differences in lags of accommodation between individuals could be due to individual calibration differences in the PowerRefractor. Examination of the residuals from the PowerRefractor calibration linear curve (Figure 1.1; mean |residual magnitude|±s.e.= 0.27±0.04) show that individual calibration differences could account for some of the individual differences observed in the lags of accommodation (approximately ±0.47D).

Large accommodative lags may be tolerated during reading in certain individuals for several reasons. High contrast and low spatial frequency content (near the peak of the contrast sensitivity function), is typically found in text and does not appear to require particularly accurate accommodation (Tucker & Charman, 1987; Ward, 1987). In myopes, hyperopic defocus has been shown to increase contrast sensitivity functions at intermediate spatial frequencies (3 c/deg) (Radhakrishnan, Pardhan, Calver & O'Leary, 2004). Theoretical variations in the ocular modulation transfer due to defocus for varying spatial frequencies

have been modeled. These models suggest that accommodative lags are likely to have little effect on the clarity of low spatial frequency gratings and therefore the lower frequency content of text (Tucker & Charman, 1987; Ward, 1987). Optical aberrations in the eye may also play an important role in a person's ability to read through significant defocus. In general, increased aberrations induce a greater depth of focus that would impart greater relative clarity to a defocused retinal image. Myopic children and young adults have been shown in numerous studies to have increased astigmatism and higher order aberrations compared to emmetropes (Cheng, Thibos, Hong, Bradley, Himebaugh, Riley & Miller, 2000; Collins, Buehren & Iskander, 2005; He, Sun, Held, Thorn, Sun & Gwiazda, 2002; Marcos, Moreno-Barriuso, Llorente, Navarro & Barbero, 2000; Simonet, Hamam, Brunette & Campbell, 1999; Sun, Sun & He, 2000), but see (Llorente, Barbero, Cano, Dorronsoro & Marcos, 2004), and may be due to poor compensation of corneal aberrations by internal optics (Benito & Artal, 2004).

Changes in the eye's aberrations during accommodation could potentially contribute to the accuracy of the accommodative response during reading. Positive spherical aberrations have been reported to become more negative during accommodation, although this change varies widely among individuals and studies (Cheng, Barnett, Vilupuru, Marsack, Kasthurirangan, Applegate & Roorda, 2004; He, Burns & Marcos, 2000; Ninomiya, Fujikado, Kuroda, Maeda, Tano, Oshika, Hirohara & Mihashi, 2002; Vilupuru, Roorda & Glasser, 2004). This change in spherical aberration has been reported to occur to a greater degree in myopes during accommodation and after sustained periods of reading (Collins et al., 2005; He et al., 2000), and may be partially secondary to lid effects (Buehren, Collins &

Carney, 2005). A negative shift in spherical aberrations during accommodation might theoretically increase the accommodative demand and could cause increased accommodative lags (He et al., 2000; Plainis, Ginis & Pallikaris, 2005). The degree of aberrations observed is proportional to accommodative lags (Collins et al., 2005; He, Gwiazda & Thorn, 2004), possibly because of an increased depth of focus. Although aberrations were not specifically measured in this study, myopes did not have increased accommodative lags, suggesting adaptations in the accommodative response.

While the dynamic characteristics of the accommodative response errors over sustained periods of reading have important implications in the treatment of myopia (e.g. reading behavior modifications), accommodative lags are only part of the accommodative behavior. Therefore, in addition to comparing the accommodative responses in progressing versus stable myopes, further study into other metrics of the accommodative response, such as variability, and their relationship to accommodative demand or subject refractive state is warranted to begin to fully understand the accommodative behavior during sustained near reading and it's possible role in the development of a refractive state.

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CHAPTER 2

VARIABILITY IN THE ACCOMMODATIVE RESPONSE DURING SUSTAINED READING

INTRODUCTION

Increased variability in the accommodative response to near targets, as in reading, has also been suggested to be a possible risk factor for the development of myopia (Harb, Thorn & Troilo, 2003; Plainis, Ginis & Pallikaris, 2005; Seidel, Gray & Heron, 2003). Variability in the accommodative response to near targets, as in reading, may be related to myopia in a number of ways. (1) Fluctuations in retinal defocus associated with accommodative variability may be a risk factor for the development of myopia (Plainis et al., 2005). Even if the mean accommodative responses shows little lag, increased accommodative variability that increases hyperopic retinal defocus during near viewing could be integrated over time and lead to myopic growth shifts (Wallman & Winawer, 2004). (2) Accommodative variability may reflect the sensitivity of accommodation to hyperopic blur, and low blur sensitivity may be a risk factor for the development of myopia if the sensitivity of the eye growth controller is also diminished. Myopes have been reported to have reduced sensitivity to retinal blur (Jiang, 1997; Rosenfield & Abraham-Cohen, 1999) which would result in larger accommodative lags since a larger amount of hyperopic blur would be required to ellicit an accommodative response and this could cause accommodation to oscillate during near viewing over a wider-than-normal range (Seidel et al., 2003). (3) The elongation of the myopic eye may affect the shape of the anterior segment and could theoretically increase

variability in the accommodative response. Mutti et al. (2000) hypothesized that increased mechanical tension on the ciliary body in the elongated eyes of myopes creates greater hyperopic lags (termed “pseudo-cycloplegia”), and accommodation has been suggested to affect eye shape as well (Walker & Mutti, 2002).

Accommodative microfluctuations are typically 0.25D in magnitude and are described as having a low (<0.6Hz) and high (1.0-2.3 Hz) frequency component (Campbell, Robson & Westheimer, 1959; Kotulak & Schor, 1986; Seidel et al., 2003; Winn, Pugh, Gilmartin & Owens, 1990a). The source of the high frequency component has been debated (Judge & Flitcroft, 2000), but is suggested to be ‘plant noise’ due to variability in zonular tension (Kotulak & Schor, 1986), arterial pulse (Owens, Winn, Gilmartin & Pugh, 1991; Strang, Winn, Gilmartin & Brosnahan, 1994; Winn, Pugh & Owens, 1990b), and crystalline lens structure (Winn et al., 1990a) during accommodation. The low frequency component, although correlated with respiration (Collins, Davis & Wood, 1995), may be involved in controlling the accommodative response to static targets (Gray, Winn & Gilmartin, 1993b; Niwa & Tokoro, 1998). The power of accommodative microfluctuations also increases at closer reading demands (Ciuffreda & Kruger, 1988).

This study was done in conjunction with an analysis of accommodative errors, as previously discussed in Chapter 1, and has the specific aim to describe variability in the accommodative response, including power spectrum analysis, over sustained periods of reading in a close-to-natural visual environment in emmetropes and myopes to determine if any relationships might exist.

METHODS

The subjects and reading task were identical to those already described in Chapter 1. The measurement of accommodation and eye position was performed with the use of the PowerRefractor, using the same measurement methods, calibration, and filtering techniques described in the previous chapter. In addition, the number of fixation breaks away from the text window was analyzed over the entire reading period.

Static Analysis of Variability-Standard Deviation

Static analysis of the variability in the accommodative response was quantified in terms of the mean standard deviation of the response for all individuals. The mean standard deviation of the accommodative response was quantified per minute of reading (ten 1-minute bins of data) to determine if any changes existed over the 10-minute reading period. The mean standard deviation of the response for the group over the entire reading period was calculated for each of the reading demands and compared to accommodative demand and subject refractive state to see if any relationships might exist.

Temporal Analysis of Variability-Power Spectrum Analysis

Pugh et al. first described the use of power spectrum analysis to quantify the temporal dynamics of ocular mechanisms (Pugh, Eadie, Winn & Heron, 1987). More recently, power spectrum analysis has been used to describe microfluctuations in the accommodative response (Campbell et al., 1959; Kotulak & Schor, 1986; Seidel et al., 2003; Winn et al., 1990b). In our study, fourier analysis was used to produce power spectra of the temporal

frequencies inherent in the accommodative response during reading. Prior to the Fast Fourier Transform a series of procedures were performed on the accommodative response data for each minute of reading. The DC component of the power spectrum was removed by performing a running average in 0.12-second increments (low pass filter). A Gaussian function was then applied to the first and last 7 seconds of data to remove high amplitude edge effects. The ten 1-minute Fast Fourier Transforms were then averaged to generate a single power spectrum for each subject (power spectrum for an individual shown in Figure 2.1) and the average power of a low (0.1 to 0.6 Hz), middle (0.61 to 0.99 Hz), and high (1.0 to 2.3 Hz) frequency component was determined at each of the three reading distances (area under the curve). The average power was then normalized for each frequency component by dividing the average power by the component's corresponding frequency width. While the low and high frequency components have been previously described (Campbell et al., 1959), we decided to quantify the middle frequency component as well to determine if any relationships to accommodation might exist.

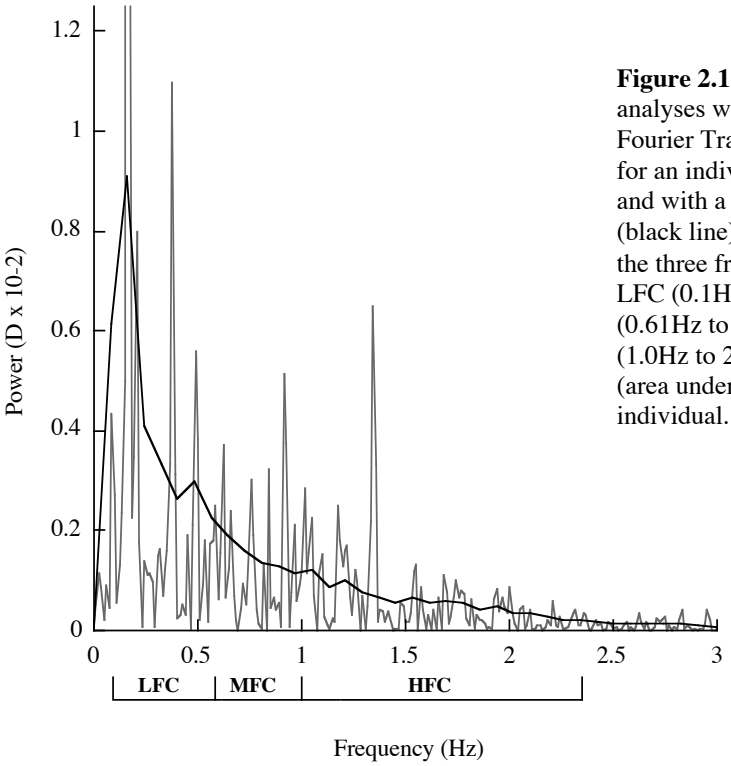


Figure 2.1- Power spectrum analyses were derived from Fast Fourier Transforms as shown here for an individual (thin grey line) and with a smoothed curve fit (black line). The mean power of the three frequency components; LFC (0.1Hz to 0.60Hz), MFC (0.61Hz to 0.99Hz, and HFC (1.0Hz to 2.3Hz) were calculated (area under the curve) for each individual.

Statistical Analysis

Repeated measures ANOVA models were used to determine if measures of accommodative variability changed over time or with different reading demands. Additionally, linear regression analysis was used to determine whether relationships existed between accommodative variability and subject refractive state. Unpaired t-tests were used to compare accommodative measures between the myopic and emmetropic groups. Statistical analysis and curve fitting was performed using Statview (Abacus Concepts, Inc., Berkeley,

CA.) and power spectrum analysis and graphical analysis was performed using Kaleidagraph (Synergy Software, Reading,PA.).

RESULTS

Standard Deviation of the Accommodative Response

The variability of the filtered accommodative response, measured as the mean standard deviation for each of the ten 1-minute periods, differed substantially among the subjects and, on average, at each of the reading demands (Figure 2.2). On average the mean variability did not change significantly over the 10-minute reading period at any of the reading demands (ANOVA: $p>0.96$ at all demands). The mean standard deviation of the accommodative response increased significantly with closer reading demands (Figure 2.2; mean±s.e.: 0.151±0.017D at 1.5D, 0.198D±0.017D at 2.5D, 0.299±0.037D at 3.5D; ANOVA $p<0.01$). The variability of the accommodative response was proportional to the amplitude of the response (Figure 2.3: $R^2= 0.38$; $p<0.01$).

Variability in the individuals' accommodative response was related to accommodative demand and to subjects' refractive state. Accommodative variability was significantly correlated with the degree of myopia at each of the three reading demands (Figure 2.4:correlations $R^2=0.49$, $p<0.01$ at 1.5D/ $R^2 = 0.31$, $p<0.05$ at 2.5D / $R^2=0.34$, $p<0.05$ at 3.5D). Furthermore, myopes showed greater accommodative variability than emmetropes especially at the closest reading demand (Mean difference at 3.5D demand= 0.14 D, unpaired t-tests: $p<0.05$).

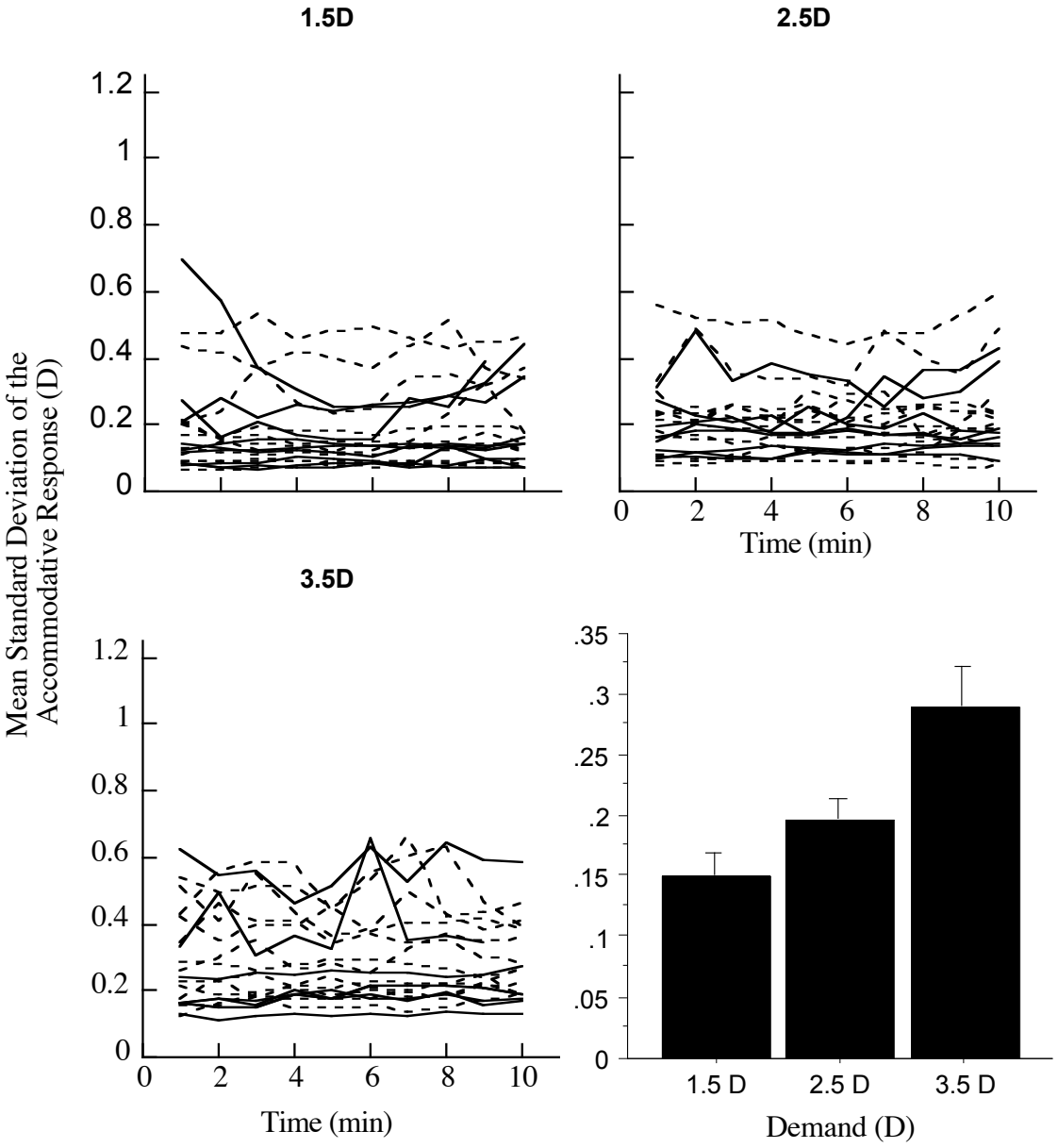


Figure 2.2 Variability of the accommodative response (measured as mean standard deviation (D)) per minute of reading differed substantially at each of the accommodative demands. Individual data are shown as thin dashed (myopes) and solid lines (emmetropes). The mean variability for the group at each of the reading demands ((Mean±s.e.) 0.151±0.017 at 1.5 D demand, 0.198±0.017 at 2.5 D demand, 0.299±0.037 at 3.5 D demand).

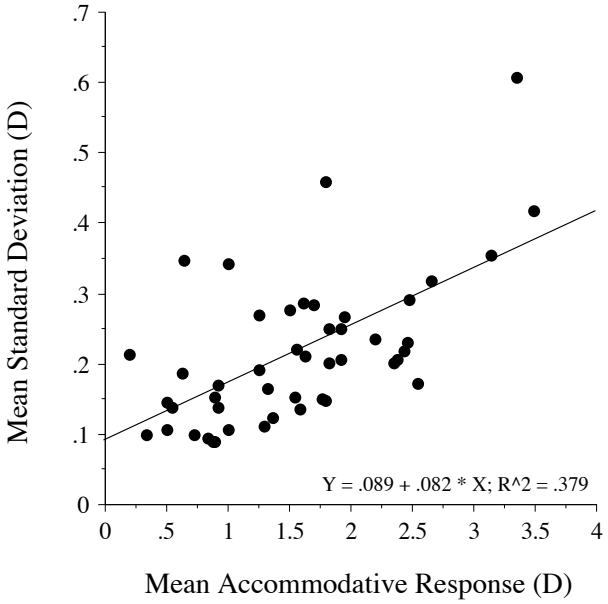


Figure 2.3 Linear regression analysis demonstrating the relationship between mean accommodative response and mean variability (s.d.) of the response for all subjects (combined data from all three accommodative demands).

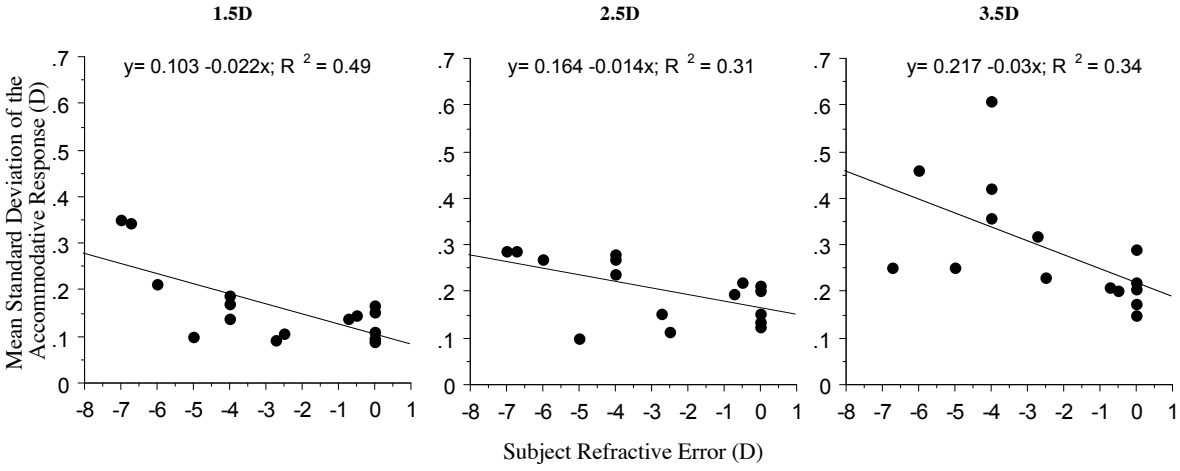


Figure 2.4 Linear regression analysis demonstrating the relationship between subject refractive error and mean variability (s.d.) of the accommodative response at each of the reading demands.

Microfluctuations

The normalized mean power (D x 10^{-2}) of all of the frequency components of accommodative microfluctuations (Table 1) increased significantly with closer reading distances (Figure 2.5; repeated measures ANOVA: LFC; $p<0.01$, MFC; $p<0.05$, HFC; $p=0.05$). In addition, the normalized power of the frequency components was highest for the LFC, which is not surprising since the low frequency component is thought to predominate in the accommodative response as it controls the error signal to static targets. The power of microfluctuations for all frequency groups was related to the subject refractive error, significantly increasing with increasing myopia at the 3.5D demand (Figure 2.6- LFC; $R^2 = 0.43$, $p<0.05$, MFC; $R^2 = 0.48$, $p<0.05$, HFC; $R^2=0.50$, $p<0.01$). This was not the case for the 1.5D and 2.5D demands.

	Demand		
Frequency Component	**1.5 D**	**2.5 D**	**3.5 D**
LFC	0.177±0.032	0.316±0.070	0.719±0.209
MFC	0.130±0.028	0.221±0.054	0.502±0.164
HFC	0.044±0.009	0.069±0.015	0.213±0.091

Table 1- The mean power (D x 10^{-2} ±s.e.) of three frequency components were calculated from individual power spectra at each reading demand by calculating the mean area under the curve of each of the three frequency component widths. The mean power of each frequency component has been normalized to the frequency width.

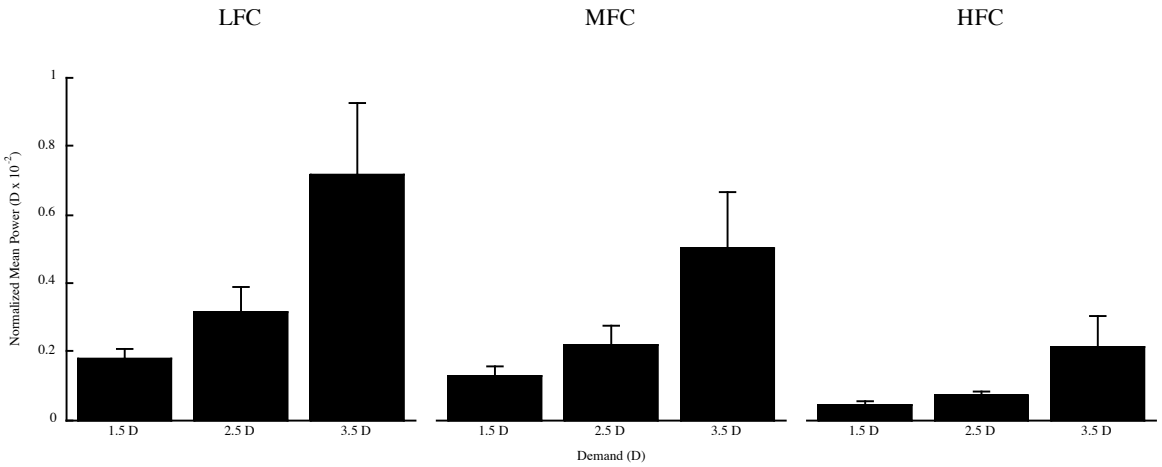


Figure 2.5 Mean power of each of the frequency components calculated from the Fourier derived power spectra for each subject at each demand (repeated measures ANOVA: LFC $p<0.01$, MFC $p<0.05$, HFC $p=0.05$). The mean power of each frequency component has been normalized to the frequency width.

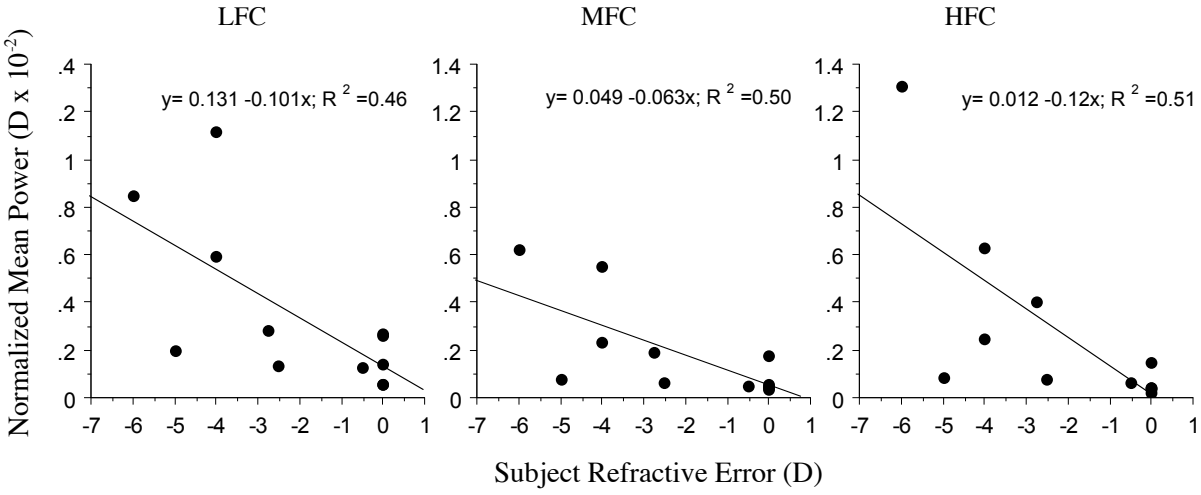


Figure 2.6 Linear regression showing a proportional relationship between subjects' refractive error and the normalized mean power of accommodative microfluctuations, for all three frequency components, at the 3.5D reading demand (Correlation LFC and MFC $p<0.05$, HFC $p<0.01$).

In the previous chapter, errors in the accommodative response during a sustained reading task in the same group of subjects were described. By comparing each individual's accommodative variability to their accommodative error, it was found that the variability in the accommodative response had an inverse relationship with accommodative lags. Figure 2.7 shows that, in general, individuals with increased accommodative lags had less variability in their response especially at the closer reading distances (correlation at 2.5D: R^2=0.22; p=0.07/ at 3.5D: R^2=0.33; p<0.05). This finding is additionally supported by the fact that individuals with higher accommodative lags tended to have less powerful accommodative microfluctuations (LFC and MFC) at the 2.5 reading distance as seen in Figure 2.8 (correlation at 2.5D LFC: R^2=0.34;p=0.06/ MFC: R^2=0.25;p=0.11). As previously stated, the high frequency component is thought to be associated with 'plant noise' of the human accommodative and physiological systems. Therefore, it is not surprising that the HFC did not have a significant relationship with accommodative lags at any of the reading distances (at 1.5D p=0.30, at 2.5D p=0.07, at 3.5D p=0.92).

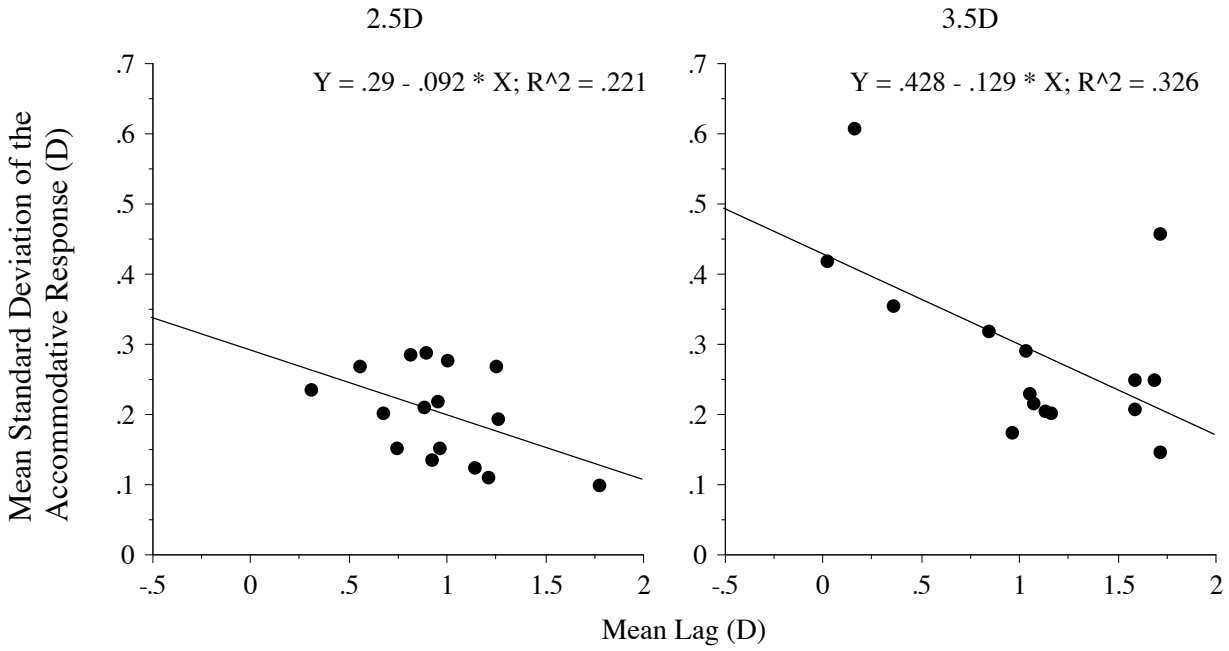


Figure 2.7- Linear regression analysis showed that the mean standard deviation in the accommodative response had an inverse relationship with accommodative lags at the 2.5D demand (p=0.06) and reached statistical significance at 3.5D (p<0.05) demand.

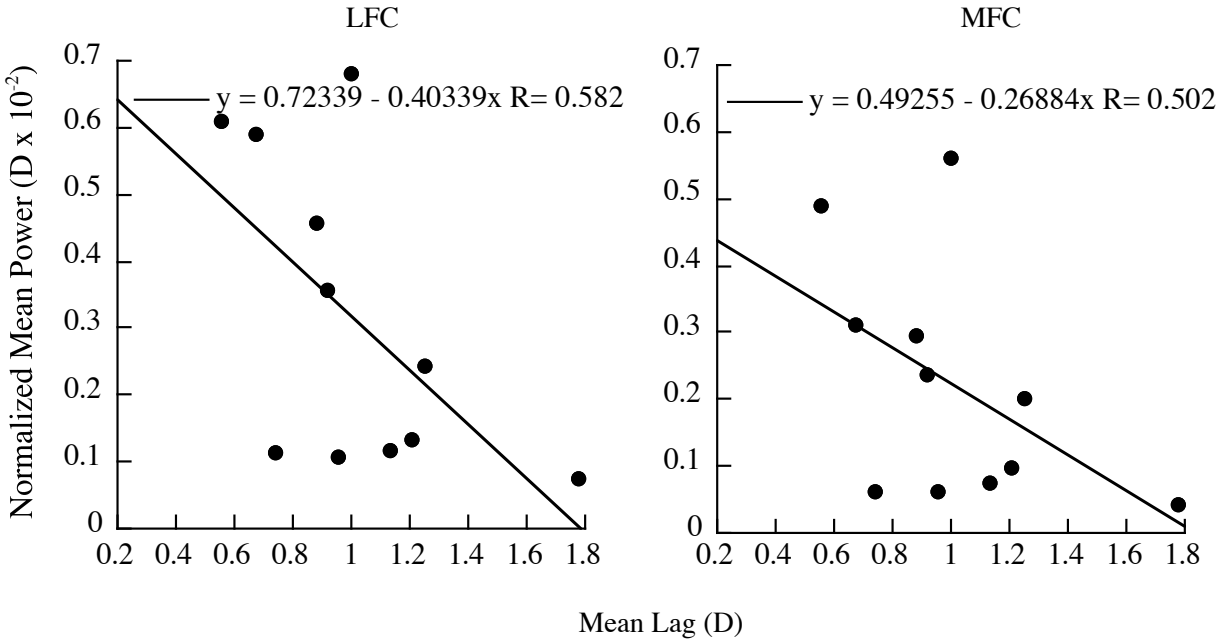


Figure 2.8 Linear regression analysis showed that accommodative microfluctuations had an inverse relationship with accommodative lags, specifically the LFC (p=0.06) and MFC (p=0.11) at the 2.5D reading demand, although not significantly.

PowerRefractor Control Experiments

Several possible sources of variability in the PowerRefractor measures were considered in a series of control experiments. Because we were concerned that the PowerRefractor measures might inherently increase in variability at closer reading distances (due to increased pixel intensity noise with steeper pixel intensity slopes), an analysis of uncorrected myopes (range: -0.25 D to -5.0 D, n=7) was performed. In this experiment, the myopic individuals were instructed to look at a distant target (high contrast 20/100 Snellen letter presented at 6m) while measures were made continuously for approximately 15 seconds. While a small but significant increase in the variability (standard deviation) of the measures with increasing myopia was found ($y= 0.07 – 0.03x$; $R^2=0.59$; $p<0.05$), it was too small to account for the increase in variability of accommodation seen at closer reading demands. In addition, to determine how much variability in the accommodative response might be due to measurement noise from eye movements during reading we performed an analysis on a sample of cyclopleged subjects (n=23) to compare the difference in the variability of measures made while fixating on a near target (isolated letter) and while reading at two near distances (28.6cm and 66.6cm). Since the subjects were unable to accommodate, their right eye was fully corrected with an appropriate trial lens for each of the near targets and an infrared filter was used over their left eye for measurement by the PowerRefractor. The difference in the standard deviation of the response between fixating and reading conditions was not significant at the 1.5D demand (mean difference in s.d.(D) = 0.06, p=0.53). At the 3.5D demand, the variability in the response was significantly less

during reading compared to fixating (mean difference in s.d. (D)= - 0.14, $p<0.05$), suggesting that eye movements during reading are not a source of increased variability.

Fixation Breaks

The number of fixation breaks during the entire reading period was analyzed for each subject. While there were substantial differences among individuals, on average there was a significant increase in the number of fixation breaks at the 3.5D demand (Figure 2.9; mean freq.±s.d.: 13.07±20.44 at 1.5D; 12.86±22.94 at 2.5D; 32.00±41.90 at 3.5D, repeated measures ANOVA: $p<0.05$). There was no significant difference in the number of fixation breaks over the three reading trial periods (mean±s.d.: =26.38±33.52 at trial 1, 22.54±39.03 at trial 2, and 10.39±4.98 at trial 3; ANOVA:$p=0.17$). Despite substantial variability, myopes had significantly fewer fixation breaks than emmetropes at the 2.5D and 3.5D reading demands (Figure 2.9; mean±s.e: myopes, 1.00±0.63; emmetropes, 28.50±11.92 at 2.5D, ANOVA $p<0.05$; myopes, 1.83±1.25 emmetropes, 46.33±19.05 at 3.5D, ANOVA $p<0.05$).

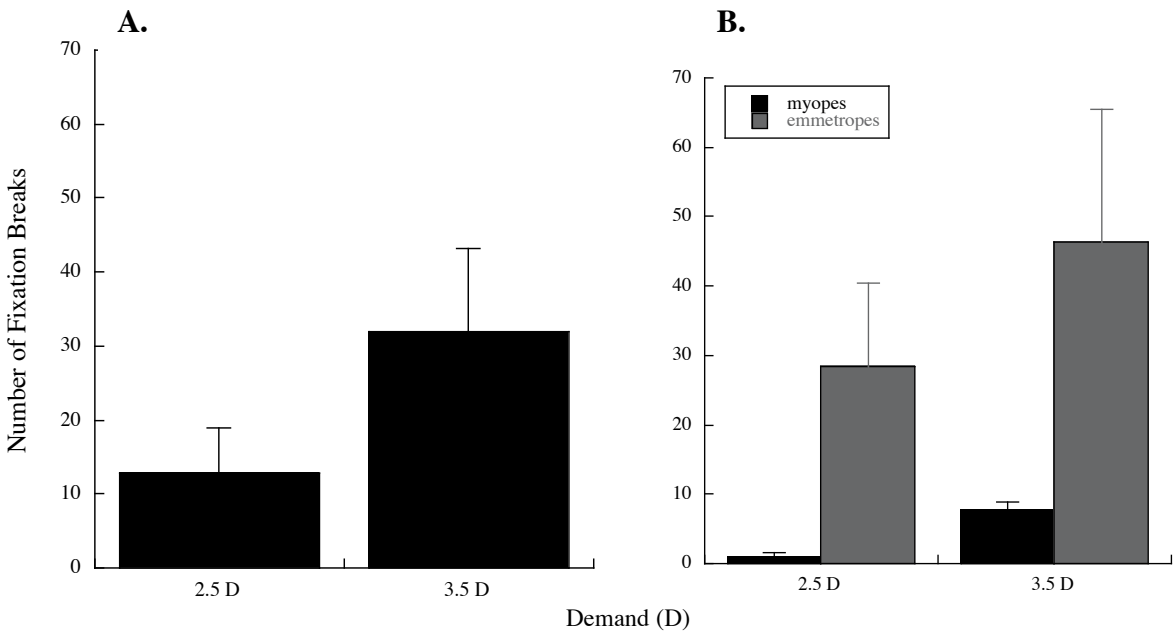


Figure 2.9 (A) The number of fixation breaks away from the text window was significantly greater at the closest reading demand (repeated measures ANOVA: $p<0.05$). **(B)** Myopes had significantly fewer fixation breaks compared to emmetropes at the 2.5D and 3.5D demands (ANOVA: $p<0.05$).

DISCUSSION

These data show that the accommodation during extended periods of reading is proportionally more variable in myopes in terms of both the standard deviation of the accommodative response and the power spectra of accommodative microfluctuations. Both measures vary greatly between individuals but, overall, show increases with increasing accommodative demand. Increases in accommodative microfluctuations have been observed with increasing accommodative demands during brief periods of accommodation (Campbell et al., 1959; Ciuffreda & Kruger, 1988; Kotulak & Schor, 1986; Plainis et al., 2005; Seidel et al., 2003) and could simply be a product of signal-dependent noise (Harris & Wolpert, 1998).

Differences in the variability of the accommodative response with subjects' refractive state however suggest a more complex relationship.

The increased variability of the accommodative response observed in myopes is suggested to be specific to the operation of the accommodation controller or possibly the accommodative plant, and not to the general increase in variability with increasing demands. In this study, both myopes and emmetropes show approximately the same average accommodative response for a given target. Therefore, accommodation in myopes appears to possess characteristics that result in greater fluctuations without increasing the average accommodative response. The explanation for this may lie in the action of the accommodative controller or the accommodative plant itself. Myopic adults have been shown to be less sensitive to defocus cues than emmetropes (Rosenfield & Abraham-Cohen, 1999; Thorn, Cameron, Arnel & Thorn, 1998), such as those used to drive accommodation, although myopic children have similar blur detection thresholds to age-matched emmetropes (Schmid, Iskander, Li, Edwards & Lew, 2002). However, the accommodative response of young myopes is reduced when their myopia starts but improves to the level of emmetropes as myopic progression slows and stabilizes (Abbott, Schmid & Strang, 1998; Gwiazda, Bauer, Thorn & Held, 1995; Nakatsuka, Hasebe, Nonaka & Ohtsuki, 2003) suggesting an adaptation process. Pairing adaptable system gain with decreased sensitivity will result in response instability in the accommodative controller, as in any servosystem. It is also plausible that the shape of the myopic eye affects the operation of the ciliary muscle and may affect the accommodative response (Mutti et al., 2000).

Increased depth of focus in progressing myopes, possibly secondary to increased higher order aberrations (Collins, Buehren & Iskander, 2005), may be responsible for blur insensitivity (Rosenfield & Abraham-Cohen, 1999), potentially leading to increased accommodative lags (Collins et al., 2005; Gwiazda et al., 1995; McBrien & Millodot, 1986; Seidel et al., 2003) and accommodative variability (Seidel et al., 2003). The variability in the accommodative response observed in our study, however, may or may not be due to differences in individuals' depth of focus. It is unlikely that pupil diameter influenced depth of focus in our subjects. The magnitude of accommodative microfluctuations and the depth of focus of the human eye (maintained at 0.30D) have been shown to be independent of pupil size (without consideration of ocular aberrations) when the pupil is greater than approximately 2.5mm (Campbell, 1957; Gray, Winn & Gilmartin, 1993a; Toshida, Okuyama & Tokoro, 1998; Tucker & Charman, 1975). The pupils of our subjects were dilated and much larger than 2.5mm diameter (approximately 5mm on average) at all reading distances therefore, increased higher order aberrations may have increased the depth of focus in our subjects. Indeed, microfluctuations of higher order aberrations have been shown to have similar frequency characteristics to accommodative microfluctuations (Zhu, Collins & Iskander, 2004) and therefore may be involved in the dynamics of accommodation during sustained reading.

It is not at all clear how increased accommodative fluctuations may relate to the development of myopia, yet several possibilities are plausible. One possibility is that temporally changing levels of defocus resulting from accommodative variability may prevent the visually guided eye growth controller from operating effectively and could result in a

default growth rate that leads to myopia. Another possibility, but one that is not mutually exclusive from the preceeding hypothesis, is that myopes are indeed generally less blur sensitive, or possess greater depth of focus, or both. In this case, myopes will not only manifest more accommodative fluctuations but will also tolerate greater accommodative lags leading to more hyperopic retinal defocus during nearwork that can drive a growth response toward myopia. Such a relationship between lags of accommodation and variability in the accommodation response was not found, however. In fact, it was found that individuals who possessed greater lags of accommodation tended to have less variability in their responses. This might be because of a change in the gain of accommodation once myopia stabilizes (Gwiazda et al., 1995), supporting the idea that that variability is dependent on accommodative output rather than the lag of accommodation. For example, in Figure 2.3 a 2D accommodative response could represent a 0.50D lag (at the 2.5D stimulus) or a 1.5D lag (at the 3.5D stimulus). There was no correlation between lag of accommodation and variability when analyzed in the same manner (ANOVA regression analysis: $y=0.263-0.051*x$;$R^2=0.041$; $p=0.17$) further suggesting that the variability in the system is dependent and proportional to the output magnitude of the physiological system. In fact, the variability increase seen with smaller accommodative lags could be predicted by the relationship of accommodative variability to accommodative response demonstrated in Figure 2.3. It could be possible that part of the variability increase seen with increased accommodation could be due to the eccentric photorefraction technique used, which multiplies the brightness slope across the vertical meridian of the pupil by a constant (conversion factor) to calculate refractions. A steeper brightness profile (more myopic) would then cause more noise, or

variability, in the measures. However, this seems unlikely to have caused the differences in variability seen at closer reading distances because the variability did not increase by a given factor (coefficient of variability; 18.64% at 1.5D; 12.30% at 2.5D; 11.91% at 3.5D). Moreover, there was no significant difference in pupil size (larger pupil produces steeper brightness profiles), between myopes and emmetropes at any of the three accommodative demands (unpaired t-test; $p > 0.16$ at all demands). We need to look at the variability of accommodation in developing myopes to further explore a possible relationship.

If increased accommodative variability and lag can affect the retinal image enough to change refractive state, then the finding that both increase significantly with closer reading demands has clinical implications. Individuals with closer reading distances may be more susceptible to myopia because the fluctuations and lags are greater. The increased blur associated with this may signal increased eye growth (Bartmann & Schaeffel, 1994; Flitcroft, 1998; Goss & Wickham, 1995; Hung & Ciuffreda, 2000; Jiang & Morse, 1999). Myopic children have habitually closer working distances than emmetropic children (Haro, Poulain & Drobe, 2000) and myopia progression is significantly greater in children with closer near working distances (Parssinen & Lyyra, 1993). Moreover, the Correction of Myopia Evaluation Trial (COMET) has recently reported that children wearing progressive addition lenses who had a lag of accommodation greater than 0.43D and a closer than normal reading distance (<31.2cm) had a significantly greater treatment effect in the reduction of myopia compared to single vision lens wearers (a 0.44 D difference over 3 years) (Gwiazda, Hyman, Norton & al., 2004). Interestingly, we observed that myopes also had fewer fixation breaks than emmetropes at the closest reading distance by a highly significant amount, suggesting

that some frequency of breaks from reading at a close distance may have a protective effect. In fact, brief periods of myopic defocus have been shown to inhibit compensatory axial growth to sustained periods of hyperopic defocus in animal models (Zhu, Winawer & Wallman, 2003).

While less is know about the middle frequency component of accommodative microfluctuations, we describe a significant relationship with increasing accommodative demand. An increase in these microfluctuations might simply reflect an inherent increase in the noise of a system with increasing output, yet the significant relationships between the MFC power and subject refractive error are contradictory. Microfluctuations within 0.61Hz and 0.99Hz significantly increased with increasing myopia and decreased with increasing lags of accommodation. Oscillations in this mid-frequency range would occur approximately once a second, therefore limiting the physiological systems that could be responsible. Careful observation of the distribution of points in the regression analyses in Figure 2.6 suggests a similar mechanism of the LFC and MFC. Therefore, one could speculate that the middle frequency component could be the tail-end of the low frequency component. Further investigation is necessary to determine the exact nature of these mid-frequency fluctuations and their specific role, if any, to accommodative behaviors.

In conclusion, the description of various accommodative behaviors during sustained periods of reading in close-to-natural near environments has been lacking. The changes in accommodative variability seen with varying reading demands and accommodative error and their relationship to subject refractive error suggest a possible relationship to the development of a refractive state. While the small fluctuations in the accommodative

response may be individually too small to stimulate eye growth, temporal integration of the fluctuations over periods of sustained reading may help to produce a causative signal. Based on our findings, closer reading distances, myopia, and smaller accommodative lags all are related to an increase in accommodative variability. Investigation in individuals with progressing ametropias, particularly children, is necessary to further define these relationships and to determine if accommodative variability during near work is involved in eye growth and the progression of a refractive state.

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CHAPTER 3

ACCOMMODATIVE BEHAVIOR IN RHESUS MACAQUES DURING SUSTAINED PERFORMANCE OF AN OPERANT CONDITIONED NEAR VISUAL TASK

INTRODUCTION

While the relationship between near work to the development of myopia has been studied for some time in humans, there has only been little evidence in animal models (Baker, Nickla & Troilo, 2002; Boisvert & Troilo, 2000; Troilo, Boisvert & Nau, 2000). Because the dynamics of accommodation can change retinal image focus, a potential factor in the control of eye growth and refractive state, we have been interested in quantifying accommodative behavior under experimental and natural conditions in humans and animals. Varying visual experiences and their relationship to eye growth has been extensively studied in animal models under experimental conditions, by examining compensatory eye growth to optical defocus imposed by lens wear (see General Overview and Chapter 1 for review). Little is known, though, about the role of more natural visual experiences in free space in these animal models and their possible influence on the development of a refractive state.

Naturally occurring myopia in animals is presumably not as common as it is in humans. Such a difference in myopia prevalence may be due to several factors including a lack of sustained near work (similar to sustained reading in humans), differences in neural adaptation processes, or differences in accommodative behaviors during near tasks. (Young, 1963) showed that rearing primates in restricted near environments caused the development

of myopia, suggesting an association with sustained periods of accommodation and near work in the development of myopia, although form deprivation effects cannot be ruled out.

This study has the aim to describe various aspects of the accommodative response, in a similar way we examined in humans, to understand the quality of vision that might be experienced during sustained near tasks in primates. This was accomplished by incorporating the examination of accommodative behaviors of the rhesus macaques while they are performing an operant conditioned free-space near viewing task over sustained periods of time. Since these monkeys can be trained to perform such visual tasks, they make an ideal animal model to study the possible mechanisms responsible for the development of myopia associated with increased near work. This work was done in collaboration with David Troilo, Ph.D. and Kristen Totonelly at The New England College of Optometry and Dolores Bradley,Ph.D. and others at the Yerkes National Primate Research Center at Emory University in Atlanta, Georgia and was presented at ARVO 2005 (Troilo, Harb, Totonelly, Merriwether & Bradley, 2005).

The operant conditioned match-to-sample task that was used in this study was originally used to serve as an extended near point task to test the hypothesis that sustained periods of near work lead to the development of myopia. Preliminary work by Bradley et al. (2002) showed that adolescent rhesus macaques who performed the task regularly seemed to develop a small myopic shift relative to normals (Figure 3.1). It was unclear, however, what the accommodative response was like in these animals while they were performing the task. Therefore, it is unknown if these animals exhibit accurate and stable accommodative responses during these sustained near tasks.

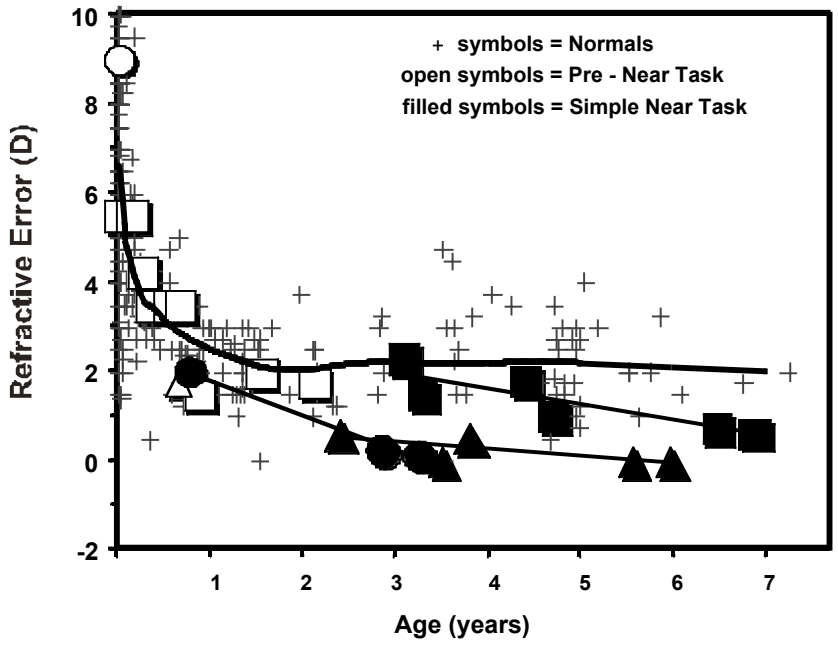


Figure 3.1 Preliminary data from Bradley et al. (2002) suggested animals that performed a near point task for extended periods exhibited a myopic shift (filled symbols) as compared to their pre-task refractions (open symbols) and to age matched normals (crosses).

METHODS

Subjects

Three adult rhesus macaques (ZZ, LI, FG) were trained at the Yerkes National Primate Research Center to perform an operant controlled visual match-to-sample task. This task is part of the monkeys' daily activities and is performed by each for approximately 1-2 hours a day for food pellet rewards. Accommodation measures were performed on these three trained adult monkeys over the course of several testing sessions. The cycloplegic refractions of the three subjects were essentially emmetropic (range: -0.25D to +1.00D), yet were reported to be relatively myopic compared to age-matched normals (Bradley, Smith, Harwerth & Fernandes, 2002).

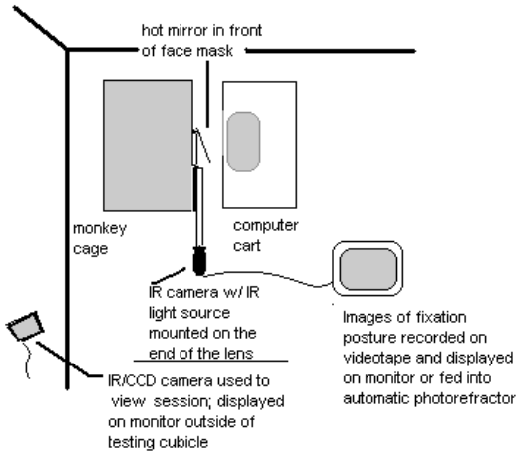
Match-to-Sample Task

The near discrimination task consisted of visual matching to a presented sample. The visual match-to-sample task requires the monkey to look at a video display terminal (maintained at eye level), which was adjustable to different working distances. The monkeys were trained to look binocularly at the display through a face-mask, which was integrated into their cage (Figure 3.2). A video camera was mounted above the cage to allow the examiner to monitor the monkeys' head placement in the face-mask. If the monkey did not consistently place their head at the plane of the face-mask, stimulus demands were adjusted for accordingly by measurements made from the video analysis. Monkeys were trained using positive reinforcement (Bioserv primate pellets) to use the joystick to control the cursor on the computer screen to indicate a response. A trial began with the presentation of a sample stimulus displayed in a random location on the computer screen. Once the monkey moved the cursor onto the sample stimulus, two additional stimuli were displayed on the screen; the monkey had to move the cursor onto the comparison stimulus that exactly matched the sample stimulus (Figure 3.3). Correct responses elicited a high-pitched tone and could be accompanied by positive reinforcement (e.g. pellets), while incorrect responses elicited a low-pitched tone and no pellet was dispensed. The number of correct and incorrect responses was recorded. The operant conditioned match-to-sample near task was performed at several near point demands (range: 20-55cm) over several testing sessions for assessment of accommodative behaviors.



Monkey in testing chamber showing monitor.

Top View of Testing Chamber





Monkey with face mask used for accommodation measures.

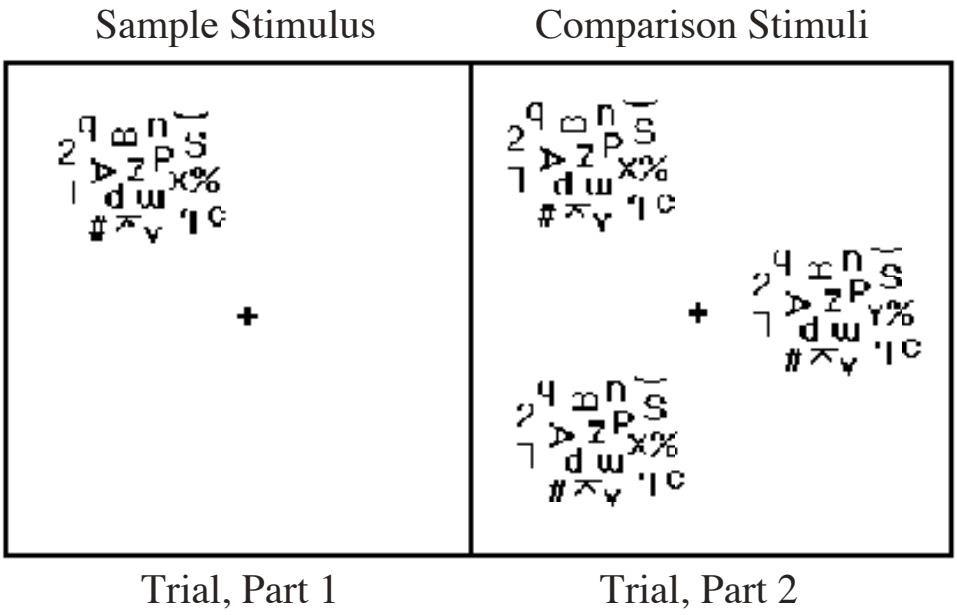


Side view showing face mask, IR hot mirror, and PowerRefractor.



Side view showing stimulus display monitor, joystick, and pellet dispenser.

Figure 3.2 Various figures describing several aspects of the testing chamber, PowerRefractor set-up, display monitor, and reward system.



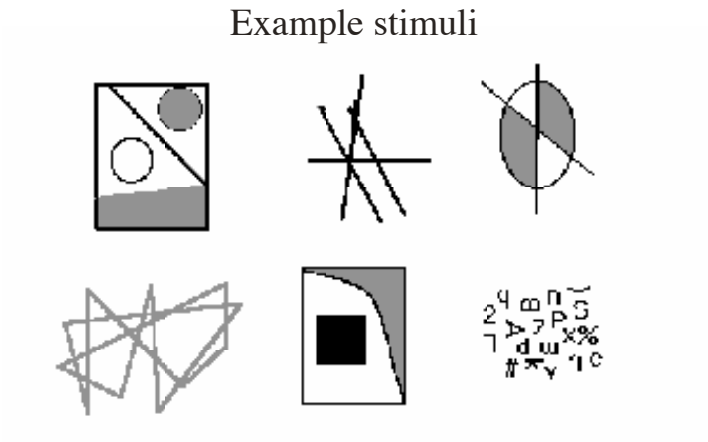


Figure 3.3 As shown above, the trial begins with the appearance of a sample stimulus on the computer screen. Using a joystick, the subject moves the screen cursor (+) to match the sample stimulus. When the cursor meets the sample stimulus, two additional stimuli appear (one matching, one different). The monkey then moves the cursor to the stimulus they believe matches and a response is recorded. If a correct response is determined, a food pellet is given as a positive reward. The figure below shows examples of various testing stimuli typically used in the near point task.

Measurement of Accommodation and Eye Position

Refractive state, pupil diameter, and eye position were measured binocularly (one eye used for accommodation analyses) at a rate of 25 Hz using an eccentric infrared photorefractor (PowerRefractor - MultiChannel Systems; Reutlingen, Germany). The refractor was positioned 1M away from the subject and was directed in between the subject's eyes, with the use of an infrared hot mirror (see Figure 3.2 for description of testing chamber). The camera's infrared light source has been established for safe use with adults and children (Choi, Weiss, Schaeffel, Seidmann, Howland, Wilhelm & Wilhelm, 2000). The PowerRefractor's built-in calibration function for rhesus macaques was used during all measures.

Gaze Filtering

Accommodation measures were filtered for eccentric gaze positions (> ±10 degrees) from the center of the stimulus monitor in order to prevent unreliable measurements from the PowerRefractor. The gaze filtering was performed on all of the accommodative measures prior to analysis. The accommodative measures corresponding to the central 10 degrees of the stimulus monitor were then analyzed as discussed below.

Analysis of the Accommodative Response

The accommodative response was analyzed offline in a number of ways to determine if any significant relationships exist between accommodative behavior and different testing distances or over the trial period. The mean accommodative response error relative to the

target demand (in terms of leads or lags of accommodation) was calculated for each subject as well as stimulus response functions and gains. The variability in the accommodative response was also quantified for each subject at all working distances. The monkeys' task responses were also recorded to quantify their accuracy in the matching task and for comparison with the accommodative response metrics measured to determine if any relationship between the accuracy of accommodation and task performance exist.

Statistical Analysis

Repeated measures ANOVA models were used to determine if the accommodative measures changed with different near working demands. Additionally, Kolmogorov-Smirnov tests were used to describe normality characteristics of the distributions of accommodation responses measured during the task, which were used to demonstrate variability in the response. Statistical analysis, curve fitting, gaze filtering, and graphical analysis were performed using Kaleidagraph (Synergy Software, Reading, PA.) and Kolmogorov-Smirnov testing was performed using Statview (Abacus Concepts, Inc., Berkeley, CA.).

RESULTS

While there were frequent breaks throughout the testing period, observation of gaze position data, as measured by the PowerRefractor, shows that on average the monkeys attend to the stimulus monitor and are on-task (Figure 3.4). Refractions measured while the monkeys were looking within the central 10 degrees of the stimulus monitor show substantial inter-subject differences at a given testing distance (Figure 3.5). The mean accommodative

error, for all stimulus distances combined, was a lag of accommodation (mean (D)±s.d.; 0.93±0.41). There was no relationship between the lag of accommodation measured and the testing distance (mean lag (D) ±s.d.; 0.98D±1.72 at 20cm, 1.11D±1.15 at 40cm, and 0.69D±1.09 at 50cm; ANOVA: p=0.28). Despite large variability in the response, accommodative stimulus response functions show that, on average, the monkeys are appropriately accommodating to the stimulus at all testing distances (Figure 3.6: average slope± s.d. = 0.989±0.162).

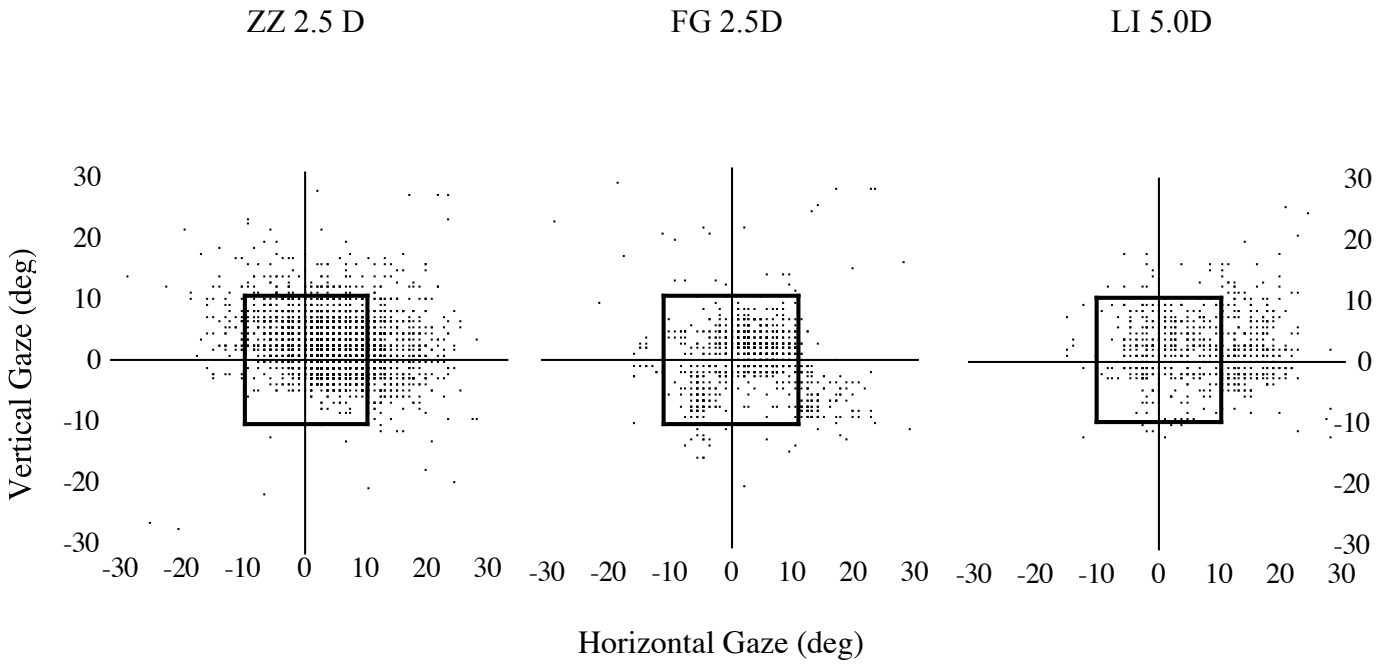


Figure 3.4 Gaze plots demonstrating all positions of gaze, as measured by the PowerRefractor, during the near visual task. The black box denotes the central 20 degrees (±10 degrees) of the stimulus monitor. Any accommodative responses which corresponded to gaze positions outside of this box were filtered prior to analysis.

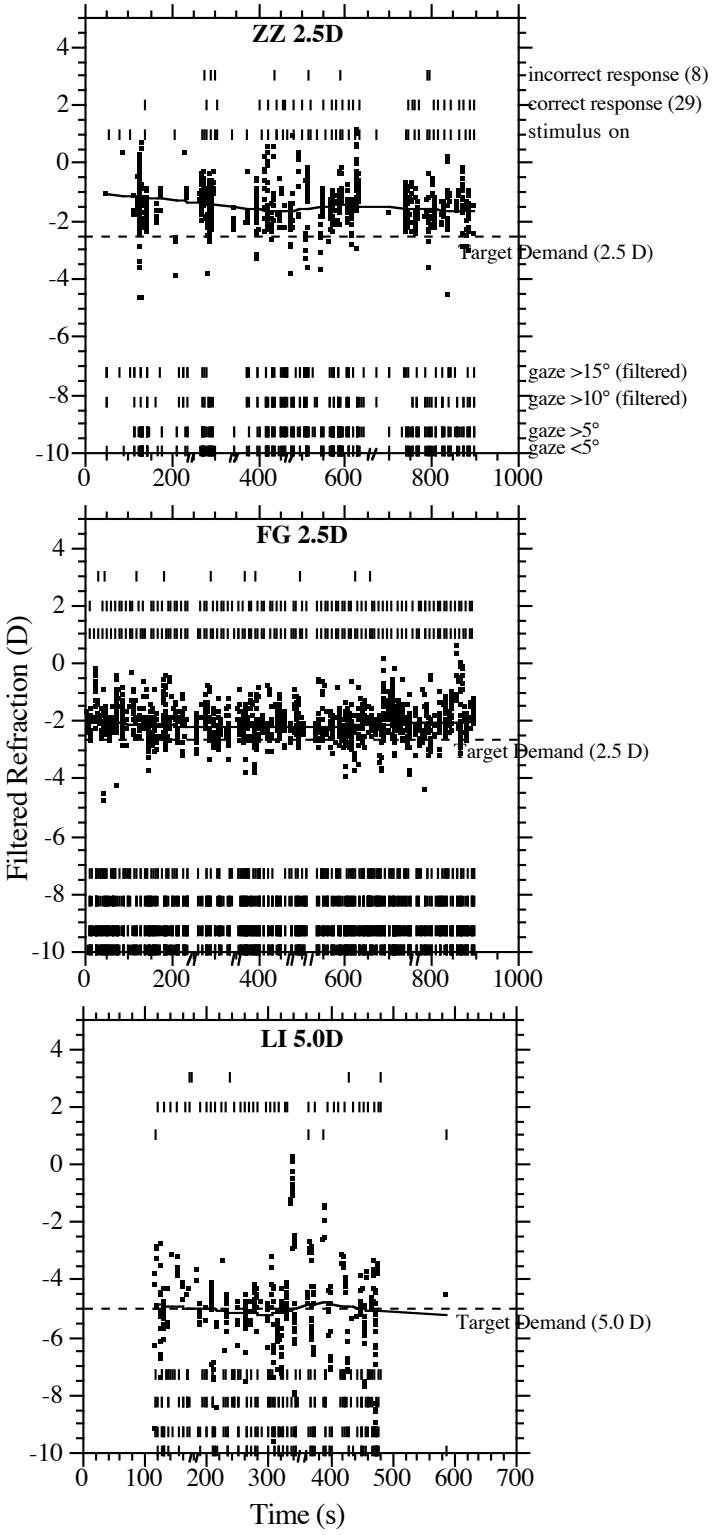


Figure 3.5 Examples of filtered refraction data for the three subjects at three different accommodative demands. The tick marks on the top portion of the graph denote when the stimulus was on and whether a correct or incorrect was made. Black closed symbols denote filtered refraction data and the solid line is a weighted mean. The dashed horizontal line denoted the target accommodative demand. The tick marks on the bottom portion of the graphs correspond to certain gaze positions during the visual task.

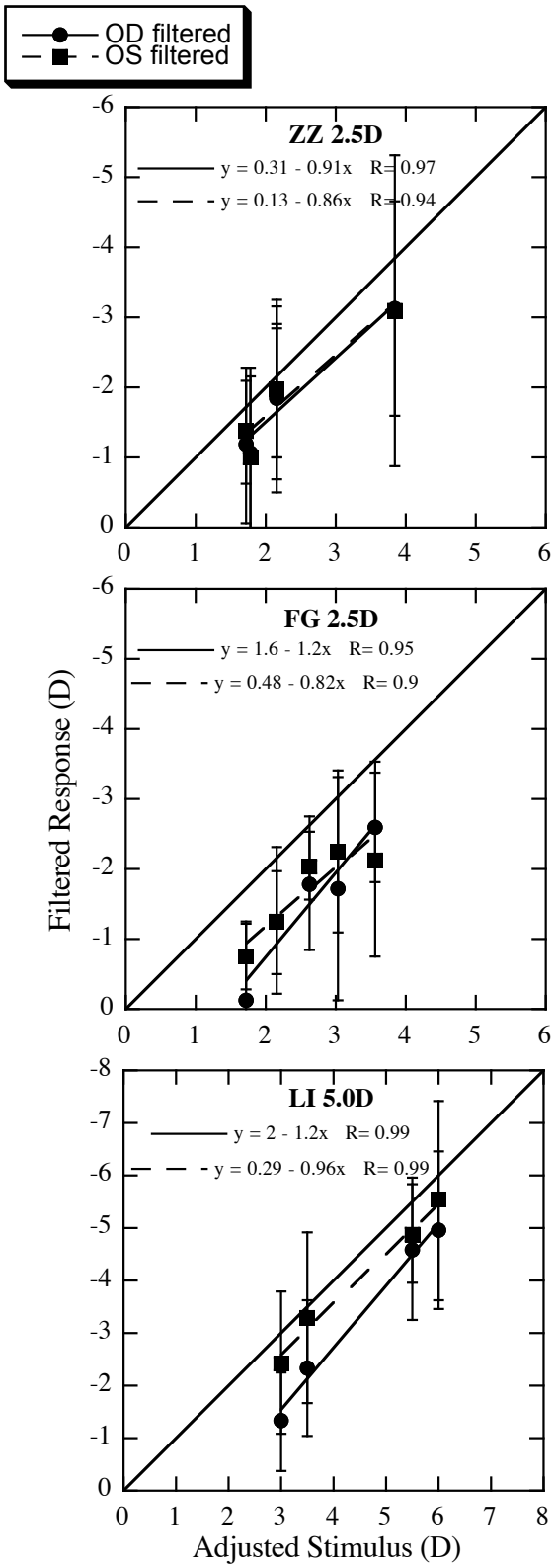


Figure 3.6 Stimulus response functions for the three subjects demonstrate appropriate shifts in accommodation for changing stimulus demands for each eye (OD=circles, OS=squares), despite substantial variability. The stimulus demand was adjusted for the subject's cycloplegic refraction and subject head placement in the face mask.

Despite variability between monkeys, on average the performance at the match-to-sample task was accurate. In general, the percentage of correct responses during accommodative measures approached 90% (Figure 3.5), even though the monkeys only spent brief periods of time looking at the stimulus monitor prior to making a match decision.

The variability of the accommodative response was substantial, as demonstrated by the wide distributions of the accommodation responses measured for each testing distance (Figure 3.7). Observation of the distributions within subjects at different testing distances shows appropriate shifts in accommodation for increasing demands. In addition, the width of the distribution of refractions measured appears to increase with increasing demand, suggesting increased variability in the accommodative response at closer near working distances. In fact, repeated measures ANOVA show a significant increase in the variability of the accommodative response, in terms of standard deviation, at closer working distances (Figure 3.8: mean s.d.(D)±s.e.= 1.72±0.26 at 20cm, 1.15±0.16 at 40cm, and 1.09±0.14 at 50cm; repeated measures ANOVA $p<0.05$).

In addition, the distributions of accommodative responses measured over the task exhibited both normal and non-normal distributions patterns (Figure 3.7). For subjects ZZ and LI, the relatively far demands show normal uni-modal distributions as demonstrated by the insignificant Kolmogorov-Smirnov testing ($p>0.83$), although FG's distribution was not normally distributed ($p<0.05$) at the further demand. At the closer working distances, some of the distributions (ZZ and FG) were not normally distributed (Kolmogorov-Smirnov: $p<0.01$), and appear to be bi-modal, suggesting two preferred states of accommodation. The

peaks of the two modes appear to rest around the stimulus demand and a resting state and the subject's distance refraction.

Analysis of the accommodative response over the entire task period, demonstrated that on average the mean state of accommodation remained fairly stable. For all subjects, the mean standard deviation of the response appeared to be significantly smaller in the first minute of the task (Mean s.d.(D)± s.e.: 0.598± 0.198; ANOVA $p<0.01$) and then increased and remained stable for the rest of the testing period (Mean s.d.(D)± s.e. in minute 2/3/4/5 respectively: 1.25±0.30/1.12±0.28/1.13±0.30/1.48±0.24; ANOVA $p>0.10$).

A comparison of the task accuracy to the accommodative response within subjects showed some differences in accommodative behavior between correct and incorrect responses, although no consistent effect was found. For example, FG accommodated significantly more prior to making an incorrect response (ANOVA $p<0.05$) than a correct one while ZZ accommodated significantly less (ANOVA $p<0.05$). There was no significant change in the standard deviation of the accommodative response between response type for any of the subjects (ANOVA $p> 0.36$).

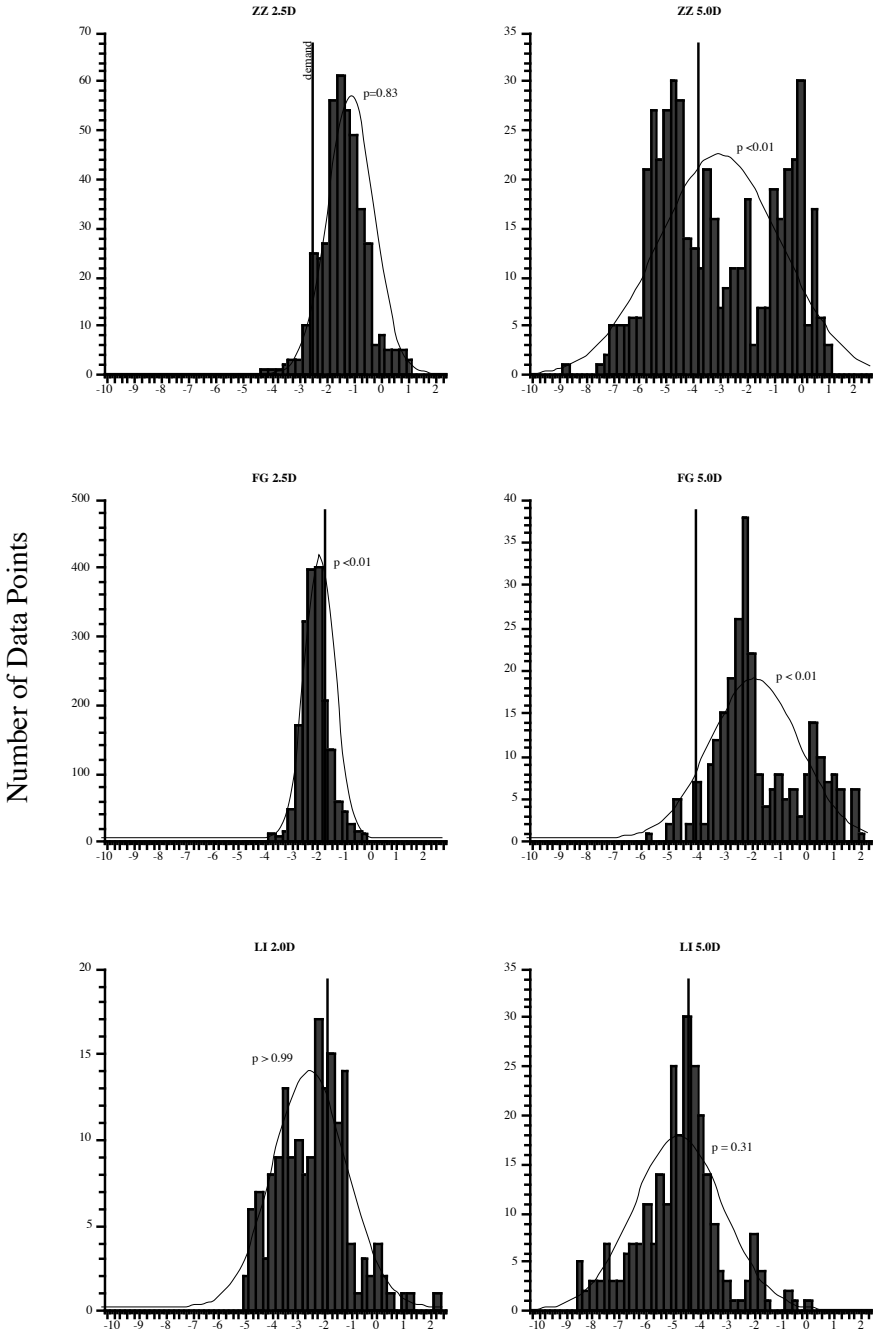


Figure 3.7 Distributions of the refractions measured during the near task were wide at both the relatively far (left distributions) and near (right distributions) conditions. The distributions demonstrate increased variability at the closer working demands and appear to be bi-modal in some subjects. Note that demand lines have been adjusted in some subjects due to head placement in the mask.

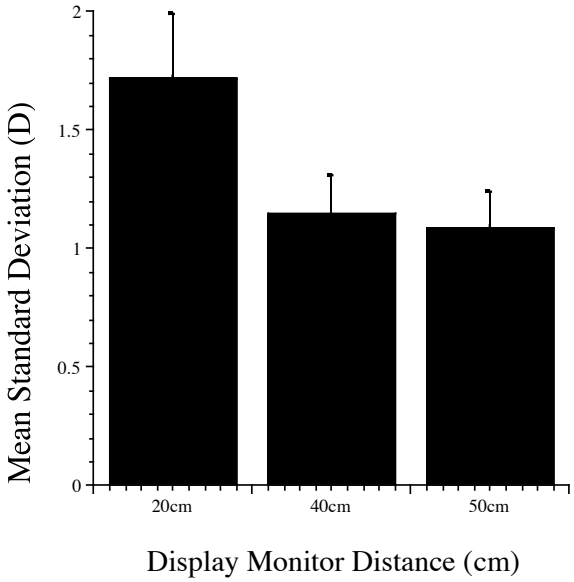


Figure 3.8 The mean standard deviation of the accommodative response significantly increased at the closer working demands (Mean s.d.(D)±s.e.= 1.72±0.263 at 20cm, 1.145±0.161 at 40cm, and 1.087±0.144 at 50cm; repeated measures ANOVA $p<0.05$).

DISCUSSION

In this preliminary study, accommodation during a near-point operant conditioned free viewing matching task in rhesus macaques was, on average, accurate, but variable over the trial period. In general, the accommodative responses of rhesus macaques were approximately twice as variable as humans at a given accommodative demand. Similar to the characteristics of human accommodation described in earlier chapters, accommodation in rhesus macaques becomes significantly more variable at close working distances, which was also exhibited by the widening of the distributions of measured accommodative responses. In some subjects, at nearer target distances, the distribution of accommodative responses measured is not normally distributed. The distributions of accommodative responses in these subjects appear to be bi-modal, suggesting two preferred refractive states during the near

task. Although these results were exhibited in only two subjects, they suggest two preferred accommodative states; active accommodation to the target and resting near the subject's refractive state.

Rhesus macaques, with appropriate training in an operant conditioned matching task, appear to make appropriate shifts in accommodation to varying target demands. Despite substantial variability, the accommodative response on average was accurate, as demonstrated by the stimulus response functions for each subject. While the average accommodative error was a lag of 0.78D for all accommodative demands combined, the subjects were remarkably accurate at the matching task. Unlike our human study, macaques showed no relationship between the magnitude of the lag of accommodation and the distance of the stimulus monitor during the near task, which might be due to the substantial variability in their responses.

Preliminary data shows that there may be differences between the magnitude of the accommodative response and response type (incorrect versus correct). Several studies in humans have shown that the accommodative response may be altered during near point tasks which impose a heightened cognitive demand (e.g. written mathematics, proofreading, etc.) (Bullimore & Gilmartin, 1988; Bullimore, Gilmartin & Royston, 1992; Kruger, 1980), possibly due to changes in the balance between sympathetic and parasympathetic activity (Birnbaum, 1984; Bullimore & Gilmartin, 1988). More subjects are needed to determine if such a relationship exists in the accommodative behavior in rhesus macaques and levels of cognitive demand in near point tasks.

While this study is preliminary, it describes the accommodative behavior in rhesus macaques during a near point free viewing visual task. Such a description of primate accommodative behavior under more habitual free-viewing conditions has not been described in the literature previously. As a counterpart to our human accommodative study, this study provides some interesting parallels in the accommodative behaviors of primates and humans under sustained periods of near work during free viewing. However, the match-to-sample task has some critical differences from a reading task including, but not limited to, a lack of sustained accommodation, sustained visual attention, and serial saccades. Despite the small sample size, some interesting relationships have been demonstrated between the accommodative behavior of rhesus macaques and the demands of the near visual task. Therefore, these results may serve as the foundation for future studies, which could further describe characteristics of the accommodative behavior in rhesus macaques during free viewing near tasks and their possible relationship to the development of induced refractive changes. Examples of future studies and analyses may include; (1) analysis of the spatial frequency content of the various near point stimuli which may uncover a relationship between accommodative accuracy and varying spatial frequencies, (2) describing the differences in accommodative responses for varying levels of cognitive demand to test the hypothesis of active versus passive accommodation in a primate model, (3) power spectrum analysis of the accommodative response to determine if rhesus macaques exhibit accommodative microfluctuations as humans do and if the fluctuations change at different near working distances, and (4) observation of possible changes in accommodative behaviors after the induction of myopia either through lens rearing or while wearing defocusing lenses.

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General Conclusions

Because of the association between reading and myopia, accommodation has been suspected to be a factor in the development of myopia. Reading is a near-work task that utilizes unique visual stimulus characteristics and requires extraordinarily long periods of visual attention, serial saccades, and accommodation to a near target. Several investigators (Abbott, Schmid & Strang, 1998; Gwiazda, Bauer, Thorn & Held, 1995; Gwiazda, Thorn, Bauer & Held, 1993; Jiang, 1997) have hypothesized that the imposed hyperopia associated with large lags of accommodation may affect eye growth and refraction in much the same way that negative lens-rearing affects eye growth and refraction in animal models (Graham & Judge, 1999; Hung, Crawford & Smith, 1995; Schaeffel, Glasser & Howland, 1988; Whatham & Judge, 2001). Although small accommodative lags during near viewing are expected because of the feedback control of the accommodative system, increased accommodative errors may worsen during near work because of optical aberrations (Buehren, Collins & Carney, 2005; Collins, Buehren & Iskander, 2005) or impoverished characteristics of the visual stimulus (Tucker & Charman, 1987; Ward, 1987) and will result in increased retinal defocus. In such cases, sustained periods of reading might make a child more vulnerable to myopia due to the consequences of degraded near visual stimuli and generally increased hyperopic defocus.

In the present study, accommodative behaviors were measured during sustained periods of near reading in a close-to-natural environment in myopes and emmetropes at several accommodative demands. Several dynamic characteristics of the accommodative behavior, including response errors and variability, were described over the entire reading

period. This study has shown that in adult subjects with stable myopia the average accommodative response lags during an extended period of reading was not significantly different than that of adult emmetropes. However, increased variability in the accommodative response, both in terms of variability around the mean and microfluctuations as identified by Fourier Analysis, was found in stable myopes, which supports several hypotheses relating increased variability to the development of myopia. Increased blur insensitivity (Rosenfield & Abraham-Cohen, 1999), possibly secondary to increased and increased mechanical tension on the ciliary body (Mutti, Jones, Moeschberger & Zadnik, 2000) have been described in myopes and may be related to an increase in accommodative variability. In addition, while the microfluctuations in the accommodative response may be individually too small or too fast to stimulate eye growth, temporal integration of the fluctuations over periods of sustained reading may be sufficient to produce a blur signal that could lead to the development of myopia (Wallman & Winawer, 2004). However, the results of this study provide no definitive conclusions as to whether temporally changing levels of defocus affect the eye growth controller or if increased variability in the accommodative response is a consequence of the myopia itself. Investigation in individuals with progressing myopia, particularly children, is necessary to determine whether these differences are risk factors for the development of myopia.

In a preliminary study, in which rhesus macaques were trained to perform an operant conditioned near visual matching task, it was shown that accommodation was not sustained while performing the task. This primate model proved useful in studying aspects of accommodative behavior under more natural free-viewing conditions. Although the macaque

sample size was small, we show that there are some similarities in the accommodative behavior of humans and primates during sustained periods of near work. For example, in both monkeys and humans the variability of the accommodative response significantly increased at closer working distances and, despite substantial lags of accommodation, the performance of a near task does not appear to be hindered. Further studies in this primate model, as outlined in Chapter 3, may provide further insight into the role of accommodative behaviors in the development of a refractive state.

In conclusion, these studies describe various dynamic aspects of accommodative behaviors during sustained near tasks in both humans and primates under close-to-natural free viewing conditions. Examining the accommodative response in this way is in contrast to typical descriptions in which the accommodative response is studied for brief periods of time under more tightly controlled viewing conditions. Although it appears that the accommodative system is fairly accurate on average, examination of the response lags and variability showed substantial inaccuracies over sustained periods of near work in both humans and monkeys. These descriptions provide a glimpse of the dynamics of the accommodative system under more natural conditions. Quantification of retinal defocus during near work may be useful in understanding the development of refractive errors and possible treatment options.

Additional work is needed to determine how the characteristics of accommodation described here might be related to other factors, such as ocular aberrations, depth of focus, or blur sensitivity and how they might interact in the development of myopia. The following future studies are proposed: (1) Longitudinal studies of accommodative behavior during

sustained near reading in children both prior to and during the development of myopia will help to determine whether variability in the accommodative response is related to the development of a refractive state or merely a consequence. If an increased variability of the accommodative response prior to myopia development is correlated with the degree of myopia then it would suggest that small amounts of retinal defocus may be temporally integrated to produce an informative signal to the eye growth controller. (2) Comparing accommodative behaviors to the magnitude of higher order aberrations in both resting and accommodative states in children and adults may uncover a relationship between increased aberration levels and reduced accommodative accuracy. If such a relationship is found in children prior to the development of myopia, then higher order aberrations and the effect they have on the accommodative response may play a role in the development of a refractive state. (3) Quantifying a subject's blur sensitivity and depth of focus and relating them to accommodative response errors and variability will lead to a better understanding of the control of accommodation and eye growth. In addition, the timing of any neural adaptations that may take place during myopia development can be explored by studying individuals with differing stable and progressing refractive errors. For example, if decreased blur sensitivity is accompanied by increased accommodative variability in individuals prior to myopia development, then the increased hyperopic defocus associated with greater depth of focus are most likely responsible for the increased eye growth. Conversely, if a reduction in blur sensitivity occurs after accommodative inaccuracies have already ensued, then the increased depth of focus might be a neural adaptation to the increased blur perceived at near.

Together, these future studies may help to build a better understanding of the complex mechanism behind the development of myopia.

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