Impact of Visual Cues on the Magnitude and Variability of the Accommodative Response in Children With Emmetropia and Uncorrected Hyperopia and Adults

Tawna L. Roberts,[1] Ruth E. Manny,[2] and Heather A. Anderson[2]

[1]Byers Eye Institute, Stanford University, Palo Alto, California, United States
[2]University of Houston, College of Optometry, Houston, Texas, United States

Correspondence: Tawna L. Roberts, Byers Eye Institute, Stanford University, 2452 Watson Ct., Palo Alto, CA 94303, USA;
tawnar@stanford.edu.

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Purpose. We investigated the effect of blur and disparity cues on accommodative accuracy (lag) and variability (time [RMS] and frequency domain [LFC]) in the developing visual system.

Methods. A total of 59 children (3–9 years, spherical equivalent refractive error [RE] = −0.3–+4.91 diopters [D]) and 10 adults (23–31 years, RE = −0.37–+1.15D) participated. Accommodation was measured in the right eye for 1 minute at 100 and 33 cm using photorefraction (25 Hz) for three conditions: blur + disparity (binocular, 20/50 optotypes), blur-only (monocular, 20/50 optotypes), disparity-only (binocular, difference-of-Gaussian stimulus). The effect blur and disparity cues have on accommodative accuracy, RMS, and LFC was assessed.

Results. Lag, RMS, and LFC increased ($P < 0.001$) from 100 to 33 cm for each condition in children and adults. In children, accommodation was most accurate and stable when blur and disparity cues remained in the stimulus and became significantly less accurate and more variable ($P < 0.001$) when blur or disparity cues were removed at 33 cm. In adults, accommodation was significantly less accurate and more variable only when blur was removed from the stimulus ($P < 0.022$). Children with RE matched to adults had less accurate and more variable accommodative responses at near than adults when cues were removed ($P \leq 0.02$).

Conclusions. In children and adults, an increase in RMS and LFC is related to an increase in accommodative lag. Children's accommodative systems do not compensate as efficiently as adults when blur and disparity cues are removed, suggesting children <10 years old do not have a mature afferent visual pathway.

Keywords: accommodation, microfluctuations, vision development, afferent visual system

The accommodative response is a product of the interactions between sensory detection of the afferent visual pathway and motor output of the efferent visual pathway.[1–3] Blur often is thought of as the afferent visual cue that drives the efferent accommodative response.[3–5] However, disparity cues also have been shown to drive the accommodative response, indicating that accommodation is driven by more than one afferent visual cue.[3,5–7]

While accommodation has been shown to be most accurate when blur and disparity cues are available,[8–10] the impact of the removal of each cue on the accommodative response remains unclear. Bharadwaj and Candy[11] found that in children and adults the accommodative response decreased more when blur cues were removed from the stimulus than when disparity cues were removed. Horwood and Riddell,[10] on the other hand, observed that the accommodative response decreased the most when disparity was removed in typically developing children and adults.

The accommodative response often is discussed in the context of accommodative accuracy, implying that accommodation is static. However, accommodation has been shown to be dynamic and oscillate around a mean response. The oscillations are referred to as accommodative microfluctuations and can be measured in time and frequency domains. Many intrinsic and extrinsic factors influence the afferent and efferent visual pathways that impact the magnitude of accommodative microfluctuations. A decrease in pupil size[12,13] and an increase in the accommodative response[14–17] have been shown to result in increased accommodative microfluctuations. Accommodative microfluctuations also have been shown to increase as luminance and image contrast decrease.[15,18] Other studies have found that an increase in the accommodative response is associated with an increase in accommodative microfluctuations, which are thought to be secondary to noise of the accommodative plant.[17] Another factor that may influence accommodative microfluctuations is whether the stimulus is viewed binocularly when disparity cues are present, or monocularly when disparity cues are removed. The effect disparity cues have on accommodative microfluctuations remains unclear as Campbell and Westheimer[19] suggested that accommodative microfluctuations may decrease under binocular viewing, while other studies have shown that viewing a stimulus monocularly in the absence of disparity cues does not systematically affect accommodative variability despite the

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observed decrease in accommodative response under monocular viewing conditions.[15,20]

Although previous reports exist of the impact of various visual cues on accommodative microfluctuations, many of these past studies have been conducted on adults and, thus, little is known about the impact of visual cues, such as blur or disparity, on accommodative microfluctuations in the developing visual system. Young children with uncorrected hyperopia are of particular interest given that they have larger accommodative demands than their emmetropic peers and have been shown to have increased accommodative microfluctuations when they accommodate to compensate for their hyperopic defocus.[21,22] Additionally, because children with larger amounts of hyperopia have greater amounts of defocus to overcome, it is important to understand the relative role of blur and disparity cues on the overall accommodative response.

When considering the impact that blur and disparity cues may have on the accuracy and stability of the accommodative response in the developing visual system, it may be useful to consider the cues in the context of the afferent and efferent visual pathways. A measured increase in the accommodative response in the presence or absence of a particular visual cue may suggest that an associated increase in accommodative microfluctuations may be due to the efferent visual pathway. However, in the context of the accommodative response, one also must consider the impact of the reciprocal increase or decrease in accommodative accuracy, which may impact the stability of the response through the afferent visual pathway.

We investigated the accommodative response in the presence and absence of blur and disparity cues to determine the relative roles that the afferent and efferent visual pathways have in generating and stabilizing the accommodative response in emmetropic and uncorrected hyperopic children aged 3 to < 10 years and adult subjects with mature visual systems.

Methods

Study Subjects

Subjects aged 3 to < 10 years and adult subjects aged 18 to <35 years were recruited from the University of Houston, College of Optometry staff, student, and patient populations, as well as the local community. The study followed the tenets of the Declaration of Helsinki and was approved by the University's institutional review board for the protection of human subjects. All subjects older than 18 years provided written informed consent and subjects younger than 18 years provided assent while their parents provided written parental permission to participate in the study.

Exclusion criteria were <32 weeks gestation, birth weight of <2500 grams, history of ocular or systemic diagnoses that may affect accommodation, taking medications known to affect accommodation, history of developmental delays or behavioral diagnoses, current or previous refractive error (RE) correction, or known cycloplegic RE ≤–0.50 diopters (D) spherical equivalent (SE), anisometropia >1.00 D SE or astigmatism >1.25 D cylinder.

All subjects underwent a complete vision examination performed by the investigator (TLR), including monocular visual acuity with isolated letters surrounded by crowding bars following the electronic psychometric visual acuity testing protocol established by the Pediatric Eye Disease Investigator Group (electronic HOTV[23,24] for subjects <8 years and Early Treatment of Diabetic Retinopathy Study [ETDRS][25] for subjects ≥8 years presented on the M&S SmartSystem (M&S Technologies, Inc. Niles, IL, USA). Subjects were excluded from data analysis if they did not have typical visual acuity for their age,[26,27] or were diagnosed with strabismus (any movement seen on unilateral cover test) or amblyopia (visual acuity > 2 lines intraocular difference in the presence of an amblyopic risk factor).[28]

Subjects also had a cycloplegic assessment of RE using the Grand Seiko WAM-5500 open-field auto-refractor (RyuSyo Industrial Co., Ltd. Hiroshima, Japan), and a dilated fundus examination. Three measures of cycloplegic RE were obtained for each eye and averaged using power vector notation.[29]

The PowerRef II (Plusoptix, Inc., Atlanta, GA, USA) was used to dynamically record accommodative responses during the experiments and only provides measures of refraction in the vertical meridian. Thus, the back-transformed mean RE from cycloplegic autorefraction in sphero-cylinder form was used to calculate the power in the vertical meridian (090) of the eye (described below) to combine the cycloplegic autorefraction and power refraction measures within each subject to calculate the total accommodative response of the subject.[22]

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

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

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

Experimental Conditions

To determine the relative importance of blur and disparity cues to the accommodative response, subjects viewed the stimuli under the following three viewing conditions at 100 and 33 cm (order randomized): (1) Blur + disparity: binocular viewing of high contrast stimulus with blur and disparity cues present, (2) Blur-only: right eye monocular viewing (left eye was occluded using a Kodak 89B Wratten gelatin filter) of high contrast stimulus to eliminate disparity cues while blur cues were preserved, and (3) Disparity-only: binocular viewing of a difference of Gaussian (DOG) stimulus (described below), which contained only low spatial frequency information to eliminate blur cues while disparity cues were preserved.[30]

The terms blur-only and disparity-only are in reference to each other since other cues, such as proximal cues, remained in the stimulus for all conditions.

Stimuli Presentation

The stimuli were displayed on an iPad Air (2048 × 1536 pixels; Apple, Inc., Cupertino, CA, USA) mounted above a beam-splitter (passes infrared light, reflects visible light) and positioned at optical distances of 33 cm (3 D demand) and 100 cm (1 D demand). Stimuli were displayed at the midline using Keynote (Apple, Inc.) presentation software. For the blur+disparity and blur-only conditions, subjects <6 years and unable to read viewed shapes, while children <6 years and able to read and children ≥6 years and adults viewed letters. Letters and shapes were scaled for each viewing distance such that they subtended 0.21° in the vertical dimension (based on lower-case letters, such as "a") at 99.7% Weber contrast through the beam splitter (stimulus, 0.02 cd/m^2; background, 5.97 cd/m^2). Letters and shapes switched every 2 seconds, with a total duration of 1 minute per experimental condition. For the disparity-only condition, subjects viewed a DOG stimulus, which was generated by calculating the difference between a broad and narrow Gaussian using the following equation:

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

where x represents the position in space in the horizontal direction (degrees) and σ represents the space constant (1.6°).

Next, the DOG was multiplied by a third luminance Gaussian to minimize edges around the border of the stimulus to further minimize the stimulus to accommodation[31] as follows:

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

where p represents the distance from the center to the border of the stimulus. The center of the DOG stimulus had a luminance of 3.5 cd/m^2. To further ensure blur cues were not visible in the stimulus, the subjects wore Rollens wraparound sunglasses (Rollens, Parker, CO, USA) during the disparity-only condition.

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

Measures of Refractive Error, Eye Position, and Pupil Size

The method of eccentric photorefraction has been described in detail previously.[32–34] Changes in RE in the vertical meridian of the eye, eye alignment, and pupil size were measured using the PowerRef II. Before experimental testing, each individual underwent a trial lens calibration for each eye to obtain more precise measures of RE.[11,32] Photorefraction data were filtered offline to eliminate outlying data points that are known to be outside of the working range of the PowerRef II or points that are unlikely to be physiologic in nature (i.e., large fluctuations secondary to a blink). Measures of RE were removed if the change in focus between two data points was $>$ 10 D/second,[35] RE measures were $<$–6.00 or $>$+4.00 D,[33,34] pupil size was $<$4 or $>$8 mm,[34] and gaze position was outside of $\pm 10°$ horizontally or $\pm 5°$ vertically.[34,36,37]

Data Analysis

The relationships between accommodative lag and accommodative variability were evaluated for each of the three conditions at the two test distances. The total amount of accommodative variability for each 1-minute trial was characterized in the time domain using root mean square (RMS)[13] and the low-frequency component (LFC)[35] using Fourier analysis from the calibrated RE measures obtained from the output of the PowerRef II from the right eye of all subjects during the accommodative tasks. Accommodative lag was calculated as mean difference between the average RE during the experiment and the accommodative demand (100 or 33 cm). The total accommodative response was calculated as the difference between the cycloplegic RE in the vertical meridian of the right eye obtained from Grand Seiko auto-refraction and the accommodative measures derived from the RE measures obtained by the PowerRef II during all conditions.[22] For example, if the average of the vertical meridian of the PowerRef II is −2.50 D and a subject has 2 D of uncorrected hyperopia obtained by Grand Seiko auto-refraction, the accommodative lag would be 0.50 D (3 − 2.50 D) and the total accommodative response would be 4.50 D (+2.00 D − (–2.50)).

Mixed (two within [distance, condition] and one between [age]) factor repeated measures ANOVA were performed for each outcome variable (accommodative lag, RMS, LFC) to determine mean differences across age (children vs. adults), distance (100 vs. 33 cm), and condition (blur+disparity, blur-only, disparity-only) with post hoc analysis (Bonferroni correction applied for within subject paired comparisons and Welch's t-test for between subject comparisons). Greenhouse-Geisser values are reported when conditions of sphericity were not met. Regression analyses (unadjusted and adjusted for pupil size and age) were performed to determine the relative contribution of the afferent and efferent visual pathways by assessing the relationship between RMS and LFC with accommodative lag and total accommodative response in the children and adults. Data from all conditions and distances were combined to provide a wide range of accommodative lags and responses for each regression analysis for the children and adults.

For all analyses that included children and adults, the analyses for children were completed twice: first using all children and second using only children with REs similar to that of the adults in an effort to isolate differences that may be due to RE and not age. All statistical analyses were performed using Stata version 12.1[38] and SPSS 25 (IBM, Armonk, NY, USA) with 2-sided statistical tests with a 0.05 significance level.

Results

Of the 76 subjects recruited to participate in the study (66 children and 10 adults), 59 children and 10 adults were included in the analyses. Of the 66 children recruited, seven were excluded from data analysis (three did not have cycloplegic RE measures, two had amblyopia, one had astigmatism $>$1.25 D, and one was born at 32 weeks gestation). Of the 59 children included in the analyses, one child did not complete the disparity-only condition at 33 cm. Of the adults who participated in the study, eight were first year optometry students who were naïve to the experiment, while the remaining two were from the community. Representative data traces for one child and one adult for each viewing condition are shown in Figure 1. Summary data for age, cycloplegic SE RE, and cycloplegic RE in the vertical meridian of the right eyes for all subjects who participated in the experiment are found in Table 1. Means and standard deviations for accommodative lag, total accommodative response, RMS, LFC, and pupil size are presented in Table 2 and box plots of the data are shown in Figure 2.

Changes in Total Accommodative Response and RMS with Increased Accommodative Demand

Mean total accommodative responses for each viewing condition were compared between the two distances tested (100 and 33 cm) to confirm that the use of two distinct testing distances with differing accommodative demands (100 cm = 1 D demand; 33 cm = 3 D demand) was successful in generating different accommodative responses for the two distances. Mean total accommodative response was significantly greater ($P < 0.001$) with Bonferroni adjustment ($P = 0.017$) at the 33 than at the 100 cm testing distance for each condition in all three groups (children, children with matched RE to adults, and adults).

Comparisons of Accommodative Lag, RMS, and LFC Across Cue Conditions and Between Children and Adults At 100 and 33 cm

Accommodative Lag. A 3-way mixed ANOVA was performed to understand the effects of available visual cues (blur+disparity, blur-only, disparity-only), stimulus distance (100 cm and 33 cm), and age group (children and adults) on accommodative lag. Changes in accommodative lag were significantly associated with visual cues available in the

Investigative Ophthalmology & Visual Science

Table 1. Summary Statistics for All Children and Adults

Group	Descriptive Variable	Mean ± SD	Range
Children, $n = 59$	Age, year	5.9 ± 1.7	3.1–9.9
	SE, D	+1.41 ± 1.08	−0.37–+4.91
	Cycloplegic RE 90 Meridian, D	+1.33 ± 1.04	−0.26–+4.66
Children, ≤1.15 D SE*, $n = 28$	Age, year	6.6 ± 1.7	3.7–9.9
	SE, D	+0.61 ± 0.40	−0.37–+1.15
	Cycloplegic RE 90 Meridian, D	+0.55 ± 0.37	−0.26–+1.13
Adults, $n = 10$	Age, year	25.3 ± 2.4	23.3–31.6
	SE, D	+0.69 ± 0.31	+0.08–+1.15
	Cycloplegic RE 90 Meridian, D	+0.67 ± 0.35	+0.06–+1.21

SE, spherical equivalent of right eye; RE, refractive error of right eye.
* Matched upper limit spherical equivalent refractive error to adults.

stimulus ($F = 16.3$, $P < 0.001$), distance the stimulus was displayed ($F = 154.2$, $P < 0.001$), and age group ($F = 8.8$, $P = 0.004$) of the subjects. A statistically significant 3-way interaction was found between visual cues, stimulus distance, and age group ($F = 3.7$, $P = 0.028$). There also was a statistically significant 2-way interaction between condition and stimulus distance in children ($F = 71.61$, $P < 0.001$) and adults ($F = 8.1$, $P = .003$). In children and adults, accommodative lag was significantly greater when the stimulus was viewed at 33 compared to 100 cm for the blur+disparity (children, $F = 53.6$, $P < 0.001$; adult, $F = 13.3$, $P = 0.005$), blur-only (children, $F = 133.3$, $P < 0.001$; adult, $F = 35.0$, $P < 0.001$), and disparity-only (children, $F = 378.4$, $P < 0.001$; adult, $F = 39.2$, $P < 0.001$) conditions. The availability of visual cues in the stimulus did not impact mean accommodative lag when the stimulus was placed at 100 cm in the children ($F = 0.7$, $P = 0.48$) or adults ($F = 0.2$, $P = 0.86$). However, when the stimulus was presented at 33 cm, the availability of visual cues did impact mean accommodative lag in both age groups (children, $F = 62.07$, $P < 0.001$; adults, $F = 8.8$, $P = 0.002$). In the children, accommodative lag became significantly larger when visual cues were removed from the stimulus. The blur+disparity condition had the smallest accommodative lag and was significantly smaller than the blur-only ($P < 0.001$) and the disparity-only ($P < 0.001$) conditions. In comparing conditions with one cue removed, the accommodative lag was significantly greater in the disparity-only condition compared to the blur-only condition ($P < 0.001$). In the adults, accommodative lag also was smallest in the blur+disparity condition, but only became statistically significantly greater for the disparity-only condition ($P = 0.02$). The blur-only condition resulted in a minimal increase in accommodative lag that was not statistically significant ($P > 0.99$). In comparing conditions with one cue removed, mean accommodative lag was 0.50 D greater in the disparity-only compared to the blur-only condition, but the difference did not reach significance ($P = 0.055$).

Table 2. Summary Values of Accommodative Lag, Total Accommodative Response, Accommodative Variability (RMS and LFC), and Pupil Size for Children and Adults

			Blur+disparity	Blur-only	Disparity-only
All Children*	Accommodative lag	100 cm	1.22 ± 0.41	1.17 ± 0.38	1.21 ± 0.56
		33 cm	1.58 ± 0.48	2.15 ± 0.65	2.66 ± 0.78
	Total accommodative response, D	100 cm	1.12 ± 0.96	1.17 ± 1.02	1.11 ± 0.93
		33 cm	2.74 ± 1.06	2.19 ± 1.20	1.70 ± 1.03
	RMS, D	100 cm	0.20 ± 0.09	0.24 ± 0.16	0.35 ± 0.19
		33 cm	0.40 ± 0.22	0.47 ± 0.24	0.65 ± 0.30
	LFC	100 cm	1.58E-03 ± 0.002	3.16E-03 ± 0.007	5.93E-03 ± 0.007
		33 cm	7.25E-03 ± 0.009	9.27 ± 0.010	2.05E-02 ± 0.02
	Pupil size, mm	100 cm	6.5 ± 0.6	6.7 ± 0.6	6.7 ± 0.6
		33 cm	6.2 ± 0.7	6.5 ± 0.6	6.5 ± 0.6
Children† ≤ 1.15 D SE	Accommodative lag	100 cm	1.14 ± 0.42	1.12 ± 0.38	1.14 ± 0.43
		33 cm	1.66 ± 0.48	2.02 ± 0.60	2.56 ± 0.73
	Total accommodative response, D	100 cm	0.41 ± 0.48	0.43 ± 0.46	0.41 ± 0.49
		33 cm	1.90 ± 0.54	1.53 ± 0.74	1.00 ± 0.77
	RMS, D	100 cm	0.15 ± 0.06	0.17 ± 0.07	0.29 ± 0.17
		33 cm	0.35 ± 0.21	0.39 ± 0.24	0.54 ± 0.22
	LFC	100 cm	8.07E-04 ± 9.1E-04	1.25E-03 ± 9.6E-03	4.61E-03 ± 7.16E-03
		33 cm	5.97E ± 7.3E-03	6.77E-3 ± 9.6E-03	1.39E-02 ± 1.4E-02
	Pupil size, mm	100 cm	6.6 ± 0.5	6.8 ± 0.5	6.8 ± 0.5
		33 cm	6.2 ± 0.7	6.6 ± 0.6	6.6 ± 0.6
Adults‡	Accommodative lag	100 cm	0.96 ± 0.21	0.99 ± 0.23	0.98 ± 0.26
		33 cm	1.31 ± 0.31	1.40 ± 0.39	1.90 ± 0.56
	Total accommodative response, D	100 cm	0.71 ± 0.48	0.68 ± 0.46	0.68 ± 0.46
		33 cm	2.36 ± 0.47	2.26 ± 0.57	1.76 ± 0.73
	RMS, D	100 cm	0.12 ± 0.04	0.11 ± 0.02	0.14 ± 0.02
		33 cm	0.19 ± 0.04	0.20 ± 0.05	0.28 ± 0.09
	LFC	100 cm	2.51E-04 ± 2.4E-04	2.24E-04 ± 1.5E-04	5.16E-04 ± 3.2E-04
		33 cm	7.10E-04 ± 4.2E-04	8.58E-04 ± 8.2E-04	2.47E-03 ± 2.0E-03
	Pupil size, mm	100 cm	6.1 ± 0.7	6.5 ± 0.6	6.7 ± 0.5
		33 cm	5.0 ± 0.5	5.9 ± 0.7	5.8 ± 0.7

mm, millimeters; cm, centimeters.
* Based on 59 children included in analysis (one child did not complete disparity-only at 33 cm).
† Based on 28 children with matched upper limit spherical equivalent refractive error to adults (one child did not complete disparity-only at 33cm).
‡ Based on all 10 recruited adults.

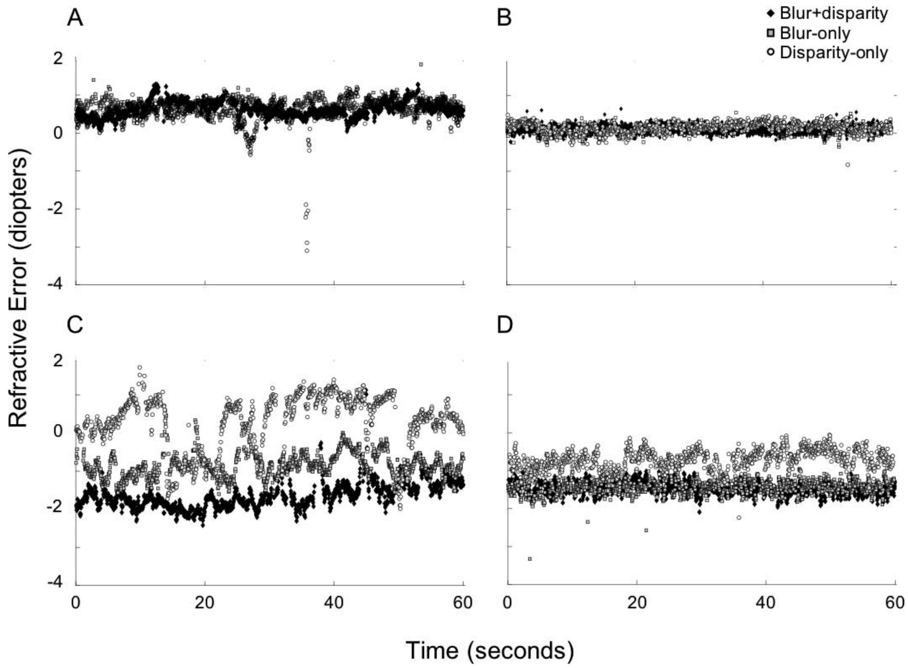

Figure 1. Sample data traces for blur+disparity, blur-only, and disparity-only conditions when the stimulus was placed at 100 cm (*top row*) and at 33 cm (*bottom row*). (**A**, **C**) A 5-year-old child with +0.60 D spherical equivalent refractive error in the right eye. (**B**, **D**) A 24-year-old adult with +0.08 spherical equivalent refractive error in the right eye.

When comparing accommodative lag between the children and adults, there was a significant main effect of age ($F = 8.8$, $P = 0.004$). A significant interaction was not detected between condition and age group ($F = 1.4$, $P = 0.25$), suggesting the differences in lag across age group were not influenced by the visual cues present in the stimulus. There was, however, a significant interaction between age group and distance ($F = 9.3$, $P = 0.003$) where the differences between groups were greatest at the 33 cm demand. Comparisons between groups showed that the children had significantly greater accommodative lags in all viewing conditions ($P < 0.03$) with the exception of the blur-only and disparity-only conditions at 100 cm (blur-only, $P = 0.054$; disparity-only, $P = 0.051$).

To explore the impact that the differences in RE between the two groups might have had on the total accommodative response between children and adults, the mixed factor repeated measures ANOVA was repeated to compare adults to a subgroup of children with RE $\leq +1.15$ D SE, the upper limit of the adults. A significant main effect of condition ($F = 21.5$, $P < 0.001$), stimulus distance ($F = 145.7$, $P < 0.001$), and age group ($F = 5.8$, $P = 0.021$) was found. The differences in lag between age groups were not dependent upon the visual cues in the stimulus, ($F = 0.9$, $P = 0.41$), but the differences remained significantly influenced by stimulus distance ($F = 9.6$, $P = 0.004$). Post hoc analyses showed that when comparing children and adults with similar upper limit RE, the children still had significantly larger accommodative lags ($P < 0.017$) in all conditions when the stimulus was displayed at 33 cm; however, no differences in lag were found when the stimuli were displayed at 100 cm ($P > 0.09$) as was found when all children were compared to adults.

Accommodative Variability. 3-way mixed ANOVA analyses were performed to understand the effects of available visual cues, stimulus distance, and age group on accommodative variability using RMS and LFC to represent variability in the time and frequency domains, respectively. Significant main effects were detected for RMS and LFC for condition (RMS, $F = 11.5$, $P < 0.001$; LFC, $F = 6.7$, $P = 0.004$), stimulus distance (RMS, $F = 44.4$, $P < 0.001$; LFC, $F = 9.8$, $P = 0.003$), and age group (RMS, $F = 22.8$, $P < 0.001$; LFC, $F = 12.2$, $P = 0.001$). A significant 3-way interaction between condition, stimulus distance, and age group was not detected for RMS ($F = 0.6$, $P = 0.95$) or LFC ($F = 0.9$, $P = 0.37$). However, the effects of condition and stimulus distance on the variability of the responses were dependent upon the age of the subjects as RMS and LFC had significant 2-way interactions between condition and age group (RMS, $F = 3.4$, $P = 0.042$; LFC, $F = 4.1$, $P = 0.02$) and distance and age group (RMS, $F = 8.1$, $P = 0.006$; LFC, $F = 6.2$, $P = 0.016$). In the children, RMS was significantly smaller and, thus, the response was more stable when blur and disparity cues were available compared to the blur-only ($P = 0.007$) and disparity-only ($P < 0.001$) conditions. RMS also was greater in the disparity-only compared to the blur-only conditions ($P < 0.001$). In the frequency domain, LFC was significantly smaller when both cues were available compared to the disparity-only condition ($P < 0.001$). Similar to RMS, LFC also was greater in the disparity-only compared to the blur-only condition ($P < 0.001$). In the adults, the response was less variable for RMS and LFC in the blur+disparity condition when compared to the disparity-only condition (RMS, $P = 0.002$; LFC, $P = 0.02$). Similar to the children, RMS and LFC were greatest in the disparity-only compared to the blur-only condition (RMS, $P = 0.003$; LFC, $P = 0.04$). When considering the distance in which the stimulus was displayed, accommodation was most variable in the time and frequency domains when the stimulus was displayed at 33 cm in children (RMS, $P < 0.001$, LFC, $P < 0.001$) and adults (RMS, $P < 0.001$, LFC, $P = 0.001$).

When comparing accommodative variability between the children and adults, as noted above, there was a significant main effect of age group for RMS ($F(1,66) = 22.8$, $P < 0.001$) and LFC ($F(1,66) = 12.2$, $P = 0.001$). Post hoc comparisons between groups showed that the children had significantly more variable responses than the adults for RMS ($P < 0.001$) and LFC ($P < 0.003$) irrespective of the cues available or the viewing distance.

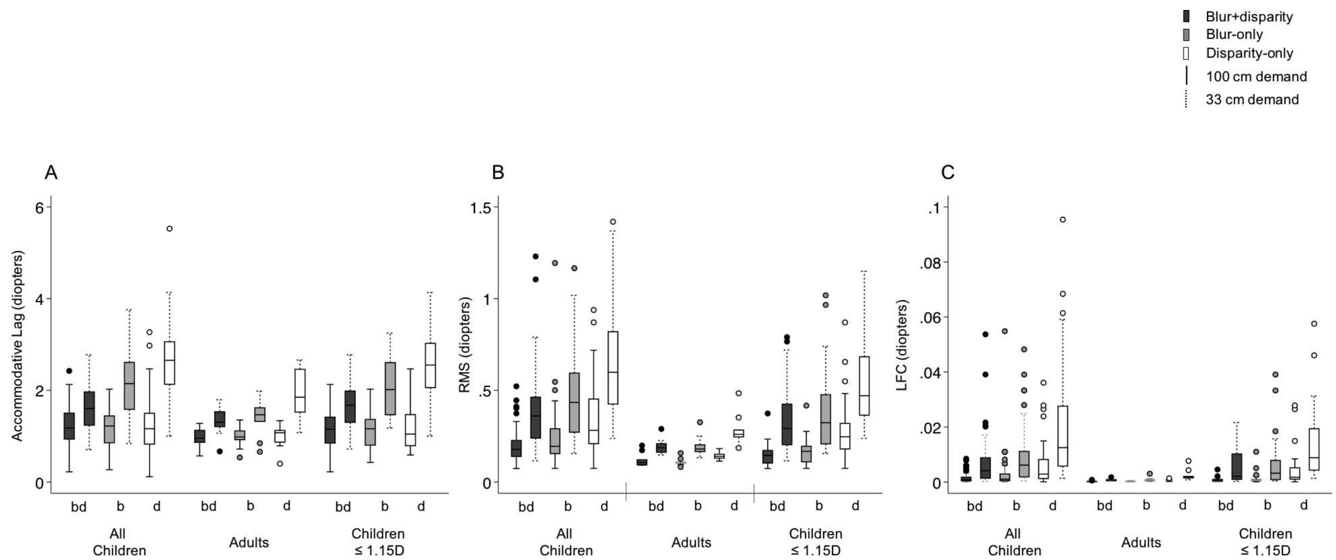

Figure 2. Box plot showing (**A**) average accommodative lag, (**B**) accommodative variability in the time domain (RMS), (**C**) accommodative variability in the frequency domain (LFC) where bd = blur+disparity, b = blur-only, d = disparity-only viewing conditions. Boxes with *solid whiskers* represent the condition at 100 cm and boxes with *dotted whiskers* represent 33 cm. There were 59 children in the 'all children' category except in the disparity-only condition where only 58 children completed the task. The adults included 10 subjects. All children with ≤1.15 D SE (upper-limit; *n*=28) participated in all viewing conditions.

A second repeated measures ANOVA was performed with the subset of children with RE ≤ +1.15 D SE, the upper limit of the adults. Significant main effects were found for RMS and LFC for condition (RMS, $F = 8.81$, $P < 0.001$; LFC, $F = 4.4$, $P = 0.03$), stimulus distance (RMS, $F = 48.5$, $P < 0.001$; LFC, $F = 10.2$, $P = 0.003$), and age group (RMS, $F = 18.6$, $P < 0.001$; LFC, $F = 12.2$, $P = 0.001$). Similar to when all children were compared to adults, post hoc comparisons showed that children had greater accommodative variability for RMS ($P < 0.002$) and LFC ($P < 0.002$) for each condition at each distance with the exception of no significant difference in RMS found between groups for the blur+disparity condition at 100 cm ($P = 0.06$).

Relationships Between Accommodative Variability and Accommodative Response, Lag, Pupil Size, Age, and Spherical Equivalent Refractive Error

Data were combined for each testing condition to determine the relationships between the outcome variables RMS and LFC and the predictor variables lag, total accommodative response, pupil size, and age. Scatter plots are shown in Figures 3 and 4, respectively. In children, RMS and LFC were significantly associated with an increase in lag (RMS, $P < 0.001$; LFC, $P < 0.001$) and response (RMS, $P < 0.001$; LFC, $P < 0.001$), and a decrease in pupil size (RMS, $P = 0.006$; LFC, $P = 0.03$) and age (RMS, $P < 0.001$; LFC, $P = 0.01$). In adults, RMS and LFC were significantly associated with an increase in lag (RMS, $P < 0.001$; LFC, $P = 0.005$) and response (RMS, $P < 0.001$; LFC, $P = 0.03$). RMS also was significantly associated with a decrease in pupil size (RMS, $P = 0.005$).

Next, the relationship between subjects' accommodative variability (RMS and LFC) and the magnitude of lag and response was evaluated using multivariable regression while adjusting for pupil size and age. The results are found in Table 3. In children, RMS and LFC were significantly associated with an increase in lag (RMS, $P < 0.001$; LFC, $P < 0.001$) and response (RMS, $P < 0.001$; LFC, $P < 0.001$). RMS also was associated with decreasing age in the multivariable model ($P = 0.02$). In adults, RMS and LFC were associated with an increase in lag (RMS, $P < 0.001$; LFC, $P = 0.01$), but an increase in response was only significantly associated with an increase in RMS ($P = 0.008$). There was no significant association ($P > 0.05$) between pupil size and RMS or LFC for the children or the adults.

To determine the relative contribution of accommodative lag and response, standardized β-coefficients also were determined in the multivariable regression analyses. As shown in Table 3, in the children, the absolute value of the accommodative lag standardized coefficient is approximately 33% greater than the standardized coefficient for response for RMS (0.45 vs. 0.30) and 38% greater for LFC (0.32 vs. 0.20). In adults, however, the absolute value of the accommodative lag coefficient is only 7% greater than the standardized coefficient for response for RMS (0.43 vs. 0.40) and 23% greater for LFC (0.35 vs. 0.27).

Discussion

The magnitude of accommodative microfluctuations has classically been thought to arise primarily in the efferent visual pathway, specifically related to physical properties of the accommodative plant.[13,17] During an increasing accommodative response, ciliary body contraction results in reduced lens zonules tension, allowing the lens to take on a more convex shape, thus, increasing the power of the lens.[39] It is thought that during an accommodative response, the greater freedom of the crystalline lens to oscillate results in greater microfluctuations.[17] Our results are in agreement with those of previous studies[14,17,40–42] that have shown that an increase in variability, in the time and frequency domains, is associated with an increase in accommodative response under similar viewing conditions (e.g., blur+disparity at 100 cm compared to blur+disparity at 33 cm), as shown in Figure 2 and Table 2. While these results support the efferent pathway hypothesis for an increase in accommodative microfluctuations given that the total accommodative response increased between the 100 and 33 cm viewing distances for all conditions, so did the lag of accommodation (Fig. 2, Table 2), which supports the afferent pathway hypothesis for an increase in accommodative microfluctuations. Greater accommodative demands have been

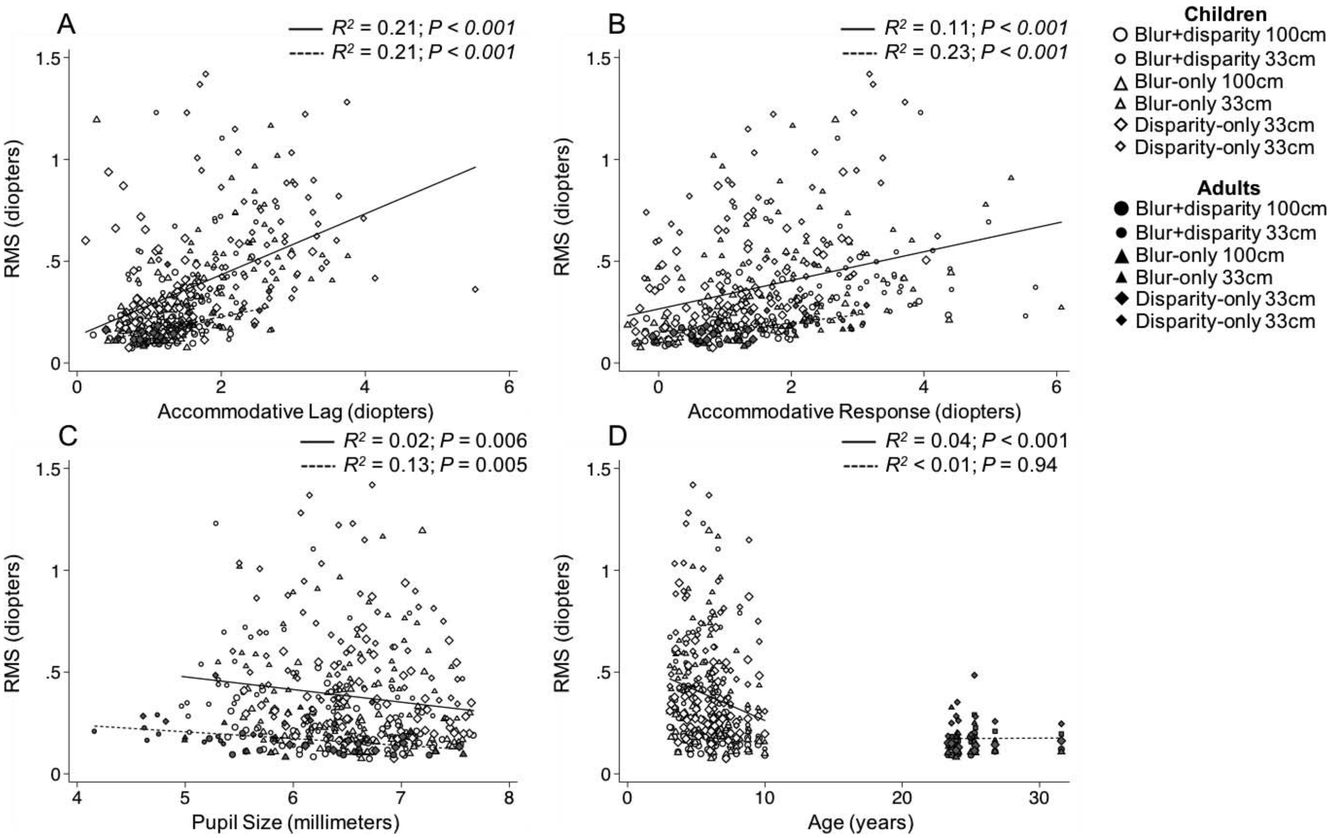

FIGURE 3. Accommodative variability in the time domain (RMS) in diopters as a function of (**A**) accommodative lag (diopters), (**B**) total accommodative response (diopters), (**C**) pupil size (millimeters), and (**D**) age (years) for children (*open symbols*, *solid regression line*) and adults (*filled symbols*, *dotted regression line*). *Large symbols* represent conditions at 100 cm and *small symbols* represent conditions at 33 cm. *Circles* represent the blur+disparity condition, *triangles* represent the blur-only condition, *diamonds* represent the disparity-only condition.

associated with larger accommodative lags in children and adults.[43–47] Higher accommodative demands, also have been associated with increases in the depth-of-focus.[42] An increase in depth-of-focus has been associated with an increase in RMS and an increase in accommodative lag.[13,42] Therefore, while it is feasible for accommodative variability to increase secondary to an efferent pathway hypothesis, as our results suggest, the afferent visual pathway may have a more influential role in the underlying etiology of accommodative microfluctuations than previously considered; even in the presence of an increase in the accommodative response.

We further investigated the visual cues of each system by evaluating the magnitude and variability of the accommodative responses during accommodative tasks at two viewing distances (stimulus at 100 and 33 cm) when blur and disparity cues were available and when either blur or disparity cues were removed from the stimulus. A difference in accommodative lag was not found across cue conditions in the children or adults when the stimuli were viewed at 100 cm where the accommodative demand was low. However, when the accommodative demand was increased by displaying the stimuli at 33 cm, the accommodative response decreased significantly in the children when disparity was removed from the stimulus and blur cues remained. The response decreased even more when blur was removed from the stimulus and disparity remained. There also was an increase in accommodative variability in the time and frequency domains that coincided with the increased accommodative lags. In the adults, there was only a significant decrease in the accommodative response in the disparity-only condition at the 33 cm demand; however, the disparity-only condition also was the only condition where the adults had a significant increase in accommodative variability (RMS and LFC) when compared to another viewing condition at 33 cm. Thus, children and adults had a similar pattern of the accommodative response being significantly more variable when there was a corresponding significant increase in accommodative lag. These results support the afferent pathway hypothesis for accommodative stability.

Our results agreed with others who have suggested that disparity is important for a more accurate and more stable accommodative response as found in the blur+disparity condition.[8–10,48] However, the relative importance of blur versus disparity in generating a more accurate and stable response is not clear. Our results agreed with those of Bharadwaj and Candy[11] as we found the accommodative response decreased when disparity cues were removed from the stimulus and blur cues remained and decreased even more when blur cues were removed and disparity cues remained. However, Horwood and Riddell[10] found that removing disparity cues from the stimulus resulted in a greater decrease in the accommodative response than when blur cues were removed. The differences across studies may be attributed to experimental design as the stimulus was static in Bharadwaj and Candy's and our study, whereas the stimulus was looming in Horwood and Riddell's study. Our results for the adults also are in overall agreement with Seidel et al.[20] as they found a small, but significant decrease in the accommodative response gradient (P = 0.046) under monocular conditions with increased accommodative demand in adults. The decrease in response coincided with a small, but insignificant increase in RMS and LFC.

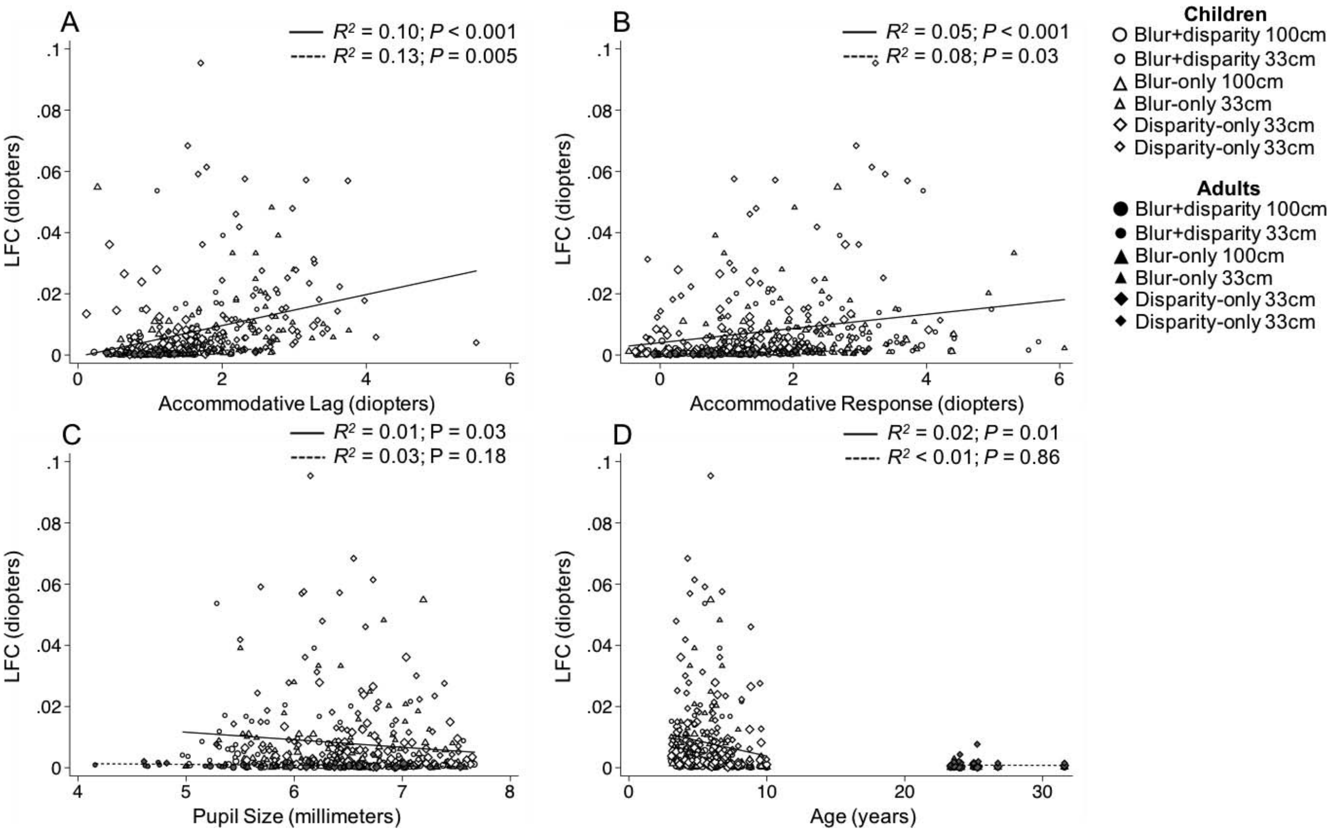

Figure 4. Accommodative variability in the frequency domain (LFC) in diopters as a function of (**A**) accommodative lag (diopters), (**B**) total accommodative response (diopters), (**C**) pupil size (millimeters), and (**D**) age (years) for children (*open symbols*, *solid regression line*) and adults (*filled symbols*, *dotted regression line*). *Large symbols* represent conditions at 100 cm and *small symbols* represent conditions at 33 cm. *Circles* represent the blur+disparity condition, *triangles* represent the blur-only condition, *diamonds* represent the disparity-only condition.

We further investigated the relative contributions of the afferent and efferent visual pathways on the variability of the accommodative response by evaluating the relationships between RMS and LFC with accommodative lag, total accommodative response, pupil size, and age in children and adults (Figs. 3, 4; Table 3). In children, univariable regression analyses showed that increase in RMS and LFC were associated with an increased accommodative lag and response as well as a decrease in pupil size and age. In adults, RMS and LFC were associated with increases in lag and response and a decrease in pupil size in RMS only. As expected, an age effect was not observed in the adults. Multivariable regression analyses revealed that in children and adults, pupil size was no longer significant in either the time or frequency domain when controlled for by the other independent variables. This is likely because the pupil size required in our study was > 4 mm and pupil size generally does not impact depth of focus or accommodative variability unless it is <4 mm.[13,49] These results also showed that in children, while an increase in RMS and LFC is associated with increased lag and response, the standardized β-coefficients suggest the largest contributor to the variability in each domain is accommodative lag (Table 3). The same trend also was seen in adults, yet the difference in contribution between the accommodative lag and response were not as large. Our data showed that as the accommodative response increases and becomes more accurate, it also is more stable, which is not consistent with the efferent pathway hypothesis. Instead, when the accommodative response decreases resulting in a larger accommodative lag, the response becomes more variable; likely due to an increase in depth of focus.[13,42] This suggests that the afferent visual pathway may contribute more to the stability of the response, particularly in children. Our data also suggest that not only are there developmental differences between children and adults, but also that developmental changes occur between 3 and 10 years of age as previously suggested.[8,21,50]

When comparing the developing visual system in children to a mature visual system in adults, the children had less accurate (i.e., greater accommodative lags) and more variable accommodative responses in the time and frequency domains than the adults in all conditions except blur-only and disparity-only conditions at 100 cm ($P = 0.054$ and $P = 0.051$, respectively). The increase in lag and variability was not likely due to the children having greater amounts of uncorrected hyperopia as the trends remained when comparing only children with similar upper limit RE to the adults (≤ 1.15 D SE), particularly at the 33 cm viewing distance. As shown in Figures 3 and 4, the relationship between RMS and LFC and age decreases with an increase in age suggesting that the afferent visual pathway is undergoing maturation between 3 and <10 years. Despite the significant relationship found between decreasing age and accommodative variability, Figures 3 and 4 show that children, as a group, do not yet have adult-like levels of accommodative variability by age 10. However, it is important to note that some children do have similar levels of accommodative behavior as the adults in each condition, although the range in behavior is more variable in children. This is particularly evident in Figure 2 as it is clear that the children have greater levels of intersubject variability in all viewing conditions. These results indicate that children express different levels of maturity in regards to the

Investigative Ophthalmology & Visual Science

TABLE 3. Results From the Multivariable Regression for Outcomes RMS and LFC in Children and Adults

Children					
		Beta Coef.	Standardized Beta Coef.	95% CI	*P* Value
RMS, *n* = 353*	Lag, D	0.15	0.45	0.12–0.18	<0.001
	Response, D	0.06	0.30	0.05–0.08	<0.001
	Pupil, mm	−0.03	−0.08	−0.07–0.005	0.09
	Ag, years	−0.02	−0.11	−0.03–0.003	0.02
	intercept	0.34	–	0.10–0.60	0.007
LFC, *n* = 353*	Lag*	5.03E-03	0.32	3.49E-03–6.56E-03	<0.001
	Response*	2.12E-03	0.20	1.09E-03–3.13E-03	<0.001
	pupil	−1.52E-03	−0.07	−3.63E-03–5.79E-04	0.16
	age2	−5.30E-04	−0.07	−1.27E-03–2.15E-04	0.16
	intercept	9.05E-03	–	−4.54E-03–2.26E-02	0.19

Adults					
		Beta Coef.	Standardized Beta Coef.	95% CI	*P* Value
RMS, *n* = 60)†	Lag, D	0.07	0.43	0.03–0.10	<0.001
	Response, D	0.03	0.40	0.01–0.06	0.008
	Pupil, mm	−0.004	−0.04	−0.03–0.02	0.78
	Age, years	0.001	0.03	−0.01–0.01	0.77
	intercept	0.04	–	−0.23–0.30	0.78
LFC (n=60)†	Lag, D	8.66E-04	0.35	2.17E-04–1.52E-03	0.01
	Response, D	3.49E-04	0.27	−9.05E-05–7.89E-04	0.117
	Pupil, mm	7.28E-05	0.05	−4.05E-04–5.51E-04	0.761
	Age, years	1.22E-05	0.02	−1.25E-04–1.50E-04	0.86
	intercept	−1.49E-03	–	−6.35E-03–3.38E-03	0.543

* Based on 353 measures from 59 children for each condition in each of the six viewing conditions except for one child who did not complete the disparity-only condition at 33 cm.

† Based on 60 measures from all 10 recruited adults in each of the six viewing conditions.

accommodative response depending on available cues, but with age, the overall maturity of cue use improves and the accommodative response becomes more homogeneous. Similar trends are seen in other aspects of vision development, such as emmetropization.[51]

As a group, the adults in this study appeared to better compensate when cues were removed under the various viewing conditions. It may be that the children are able to integrate across cues, but are unable to compensate as efficiently as adults when cues are removed from the stimulus, suggesting a more mature afferent visual pathway in adults. Possible sources for the differences in accommodative lag and variability in the children may arise also from the children's depth-of-field and children's ability to detect blur, another possible afferent explanation for the mechanism to stabilize the accommodative response. Considering accommodative variability in the context of serving as a subthreshold blur detector,[52] if children have larger depths-of-field than adults, then accommodation is able to fluctuate at greater magnitudes, as demonstrated by previous studies showing increased RMS with increased DOF.[13,21] Likewise, it has been shown that children have a decreased ability to detect blur, and, thus, accommodation would be able to be more variable without impacting the perception of blur.[21]

Children's accommodative systems being less able to compensate for the removal of visual cues may be particularly consequential in children with amblyopia or strabismus. Manh et al.[53] found that in children with unilateral amblyopia, the fellow eye (i.e., nonamblyopic eye) had greater accommodative errors when comparing the accommodative response to the better seeing eye in typically developing children without amblyopia. In their study, 52% of children with amblyopia did not have measurable stereopsis (worse than 800″) and, thus, were not likely to be using disparity cues to help drive the accommodative response. Children with amblyopia and strabismus may also be more likely to have more variable accommodative responses, particularly children with amblyopia, as they have greater depth of focus and, as discussed above, increased accommodative microfluctuations have been shown to be associated with greater depth of focus. However, to the authors knowledge, accommodative microfluctuations have yet been studied in children with strabismus or amblyopia in a systematic investigation. However, Ukai et al.[54] observed that half of the children with amblyopia (strabismic and anisometropic amblyopia) in their study ($n = 17$) had increased accommodative microfluctuations during an accommodative task. Thus, more investigation is needed to understand the full consequences of the immaturity of the developing visual system in processing visual cues, particularly in children with or at risk for strabismus and amblyopia.

Study Limitations

Our study is not without limitations. The first limitation of the study is that cycloplegic SE was measured on the Grand Seiko auto-refractor, whereas all experimental measures were captured using the PowerRef II.[22] Most children had dilated pupil sizes of >8 mm, which is outside of the operating range of the PowerRef II and, thus, cycloplegic measures were taken using the Grand Seiko. Additionally, four subjects had levels of uncorrected hyperopia that were outside of the operating range of the PowerRef II if measured under cycloplegia. While two separate instruments were used for data collection, a recent study has shown that the Grand Seiko is comparable to subjective refraction[55] suggesting that we used an appropriate value for SE. It also has been shown that the PowerRef II and Grand Seiko

Investigative Ophthalmology & Visual Science

are comparable when static accommodative measures are obtained at 40 cm,[55] and that the PowerRef 3 (increased sampling rate from the PowerRef II) and Grand Seiko are comparable when dynamic accommodative measures are obtained simultaneously at accommodative demands ranging from 20 cm to 3 m (Gehring AM, et al. *IOVS* 2018;59: ARVO E-Abstract 2950). Also, it should be noted that while relative lens calibrations were performed to account for intersubject variability in the luminance slope change per diopter, absolute calibrations (absolute offset) were not performed, which introduces an additional limitation to our data analysis regarding accommodative lag and response. Previous authors typically analyzed accommodative lag using photorefraction with one of two methods described here. The first method calculates a relative change in accommodation from one distance to another and relies on the assumption that the subjects fully relax accommodation at the distance stimulus. Given that we were specifically interested in children with a large range of uncorrected hyperopia, it would be incorrect to assume that accommodation would be fully relaxed for distance, or even that accurate focus was obtained for the distance stimulus. The second method applies an absolute calibration factor obtained from cycloplegic or dynamic retinoscopy on a control group to future experimental data from a different subject set. The applied calibration factors are not obtained during simultaneous viewing for the calibration method (cycloplegic or dynamic retinoscopy) along with PowerRefractor and often not under the exact same viewing conditions. While an absolute calibration was not determined in a control group in this study, we did evaluate the application of the calibration factor used by Harb et al.[35] to our data. Adjusting refractive data by this previously published calibration factor did not change the results of the ANOVA comparisons or regression analyses with the one exception of the relationship between RMS and total accommodative response in the multiple regression analysis for adults (calibrated data suggested total response was not significantly associated with RMS when controlled for all other variables). Thus, we do not believe this limitation in study design impacted the conclusions drawn from the data. Our decision to accept this limitation is further supported by findings that the PowerRefractor (Multichannel Systems version – predecessor to the PowerRef II – 25Hz) compares well to retinoscopy (mean difference = –0.28 D [range, –0.43–0.05 D])[56] and the Grand Seiko autorefractor (mean difference at a 2.5 D demand = 0.08 ± 0.32 D; mean difference at a 5 D demand = –0.32 ± 0.48 D),[55] and, thus, we feel that any errors from lack of offset calibration would be small and have minimal impact on our results.

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

Summary and Conclusions

The results of our study suggest that an underlying afferent pathway hypothesis may be contributing to the stabilization of the accommodative response in addition to the previously proposed efferent pathway hypothesis. Our results also demonstrated that there appears to be a difference in the afferent visual pathway between children and adults. In children, accommodative accuracy decreased while accommodative variability increased when blur and disparity cues were systematically removed from the visual stimulus at 33 cm, whereas in adults there was only a decrease in accommodative accuracy and coinciding increase in accommodative variability when blur cues were removed from the stimulus. Thus, it appears that children are able to integrate across cues, but are unable to adapt as efficiently as adults when cues are removed from the stimulus, suggesting that on average, children do not have a mature afferent visual processing system by 10 years of age.

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