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Pupil responses to near visual demand during human visual development

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Abstract

Pupil responses of adults to near visual demands are well characterized but those of typically developing infants and children are not. This study determined the following pupil characteristics of infants, children and adults using a PowerRefractor (25 Hz): i) binocular and monocular responses to a cartoon movie that ramped between 80 and 33 cm (20 infants, 20 2–4-yr-olds and 20 adults participated) ii) binocular and monocular response threshold for 0.1 Hz sinusoidal stimuli of 0.25 D, 0.5 D or 0.75 D amplitude (33 infants and 8 adults participated) iii) steady-state stability of pupil responses at 80 cms (8 infants and 8 adults participated). The change in pupil diameter with viewing distance (Δpd) was significantly smaller in infants and 2–4-yr-olds than in adults ($p < 0.001$) and significantly smaller under monocular than binocular conditions ($p < 0.001$). The 0.75 D sinusoidal stimulus elicited a significant binocular pupillary response in infants and a significant binocular and monocular pupillary response in adults. Steady-state pupillary fluctuations were similar in infants and adults ($p = 0.25$). The results suggest that the contribution of pupil size to changes in retinal image quality when tracking slow moving objects may be smaller during development than in adulthood. Smaller monocular Δpd reflects the importance of binocular cues in driving near-pupillary responses.

Keywords

accommodation; blur; consensual; depth-of-focus; disparity; hippus; pupil; vergence; visual development

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Introduction

Clear and single visual experience is a pre-requisite for normal postnatal visual development (Donahue, 2005; Fielder & Moseley, 1996; Harwerth, Smith, Duncan, Crawford, & von Noorden, 1986; Hubel & Wiesel, 1965; Kiorpes et al., 1987; Movshon et al., 1987). The developing visual system achieves this under naturalistic binocular viewing conditions by generating accommodative and vergence responses that are appropriate for the stimulus demand (Banks, 1980; Bharadwaj & Candy, 2008; Howland, Dobson, & Sayles, 1987; Turner, Horwood, Houston, & Riddell, 2002). The third component of the near triad, the pupil, also plays a role in determining the quality of the retinal image during near fixation. Pupillary constriction in response to a change in fixation from distance to near reduces the size of the point spread function and improves retinal image quality for adults (Campbell, 1957; Charman, 1983; Charman & Whitefoot, 1977; Westheimer, 1964). This increases the optical depth-of-focus (DOF), thereby reducing the demand on accommodation to maintain clear vision (Ward & Charman, 1985, 1987). The change in the optical DOF with pupil size is quite nonlinear, with the DOF increasing dramatically for pupil diameters smaller than 3 mm (Charman & Whitefoot, 1977). Overall, synchronous changes in accommodation, vergence and pupil size allow the visual system to achieve binocular clear and single vision in the dynamic three-dimensional environment (Loewenfeld, 1993a; Marg & Morgan, 1949, 1950).

Unlike accommodation and vergence, little is known about near pupil responses during early visual development. The baseline pupil diameter under ambient light levels is about 5.5 to 5.7 mm in 6 to 9-month-old infants and gradually increases with age to reach adult-like levels (6.8 to 7.5 mm) by 9 to 10 years of age (MacLachlan & Howland, 2002). Schaeffel, Wilhelm, and Zrenner (1993) and Wilhelm, Schaeffel, and Wilhelm (1993) observed no significant change in pupil diameter in 5 to 10-year-olds when they changed fixation from distance to a near target (4 D or 10 D). Pupillary constriction for the same near visual demand was up to 1 mm per diopter in adults, with large inter-subject variability (Schaeffel et al., 1993). Gislén, Gustafsson, and Kroger (2008) also observed that the pupillary constriction of 9- to 10-year-old children (1.47 mm for a 6 D accommodative demand) was significantly smaller than that of adults (1.83 mm for the same accommodative demand), while Schafer and Weale (1970) observed that a small number of older, 10 to 13-year-olds, had adult-like reduction in pupil diameter at near. Near pupil responses of children less than 4-yr of age have not been investigated previously and hence the role of their pupil in determining retinal image quality during near vision remains unknown.

Children's pupil responses were measured under naturalistic binocular viewing conditions in the previous studies, with all sensory cues (e.g. retinal blur, disparity, target proximity, etc) consistent with each other (Gislén et al., 2008; Schaeffel et al., 1993; Schafer & Weale, 1970; Wilhelm et al., 1993). When binocular cues are removed during monocular viewing, accommodative and vergence performance deteriorate significantly in infants and children, suggesting that binocular cues are important in generating appropriate near motor responses (Bharadwaj & Candy, 2008, 2009; Turner et al., 2002). Binocular cues might, therefore, also influence the characteristics of near pupillary responses. The first aim of this study was to characterize the binocular and monocular pupil responses of typically developing <1-yr-old infants, 2 to 4-yr-old children and adults to gradual changes in near visual demand.

The visual system's sensitivity to target distance (i.e. the smallest change in target distance that would elicit a reliable motor response) is fundamental to generating accurate motor responses at near. The sensitivity of the 3-month-old infant accommodative system appears to be at least 0.5 D for binocular viewing and 0.75 D for monocular viewing, while that of adults was found to be at least 0.25 D (the smallest stimulus used) for both viewing

conditions (Wang & Candy, 2010). Adult sensitivities as small as 0.1 D have been observed in other studies using different experimental conditions (Kotulak & Schor, 1986; Winn, Charman, Pugh, Heron, & Eadie, 1989). The sensitivity of the other two components of the near-triad—pupil and vergence—have not been determined thus far. The second aim of this study was to determine the sensitivity of the infant pupillary system and compare it to that of adults by measuring pupil responses to small (0.25 D, 0.5 D and 0.75 D) sinusoidal changes in target distance.

The third aim of the study was to compare pupillary hippus (i.e. the steady-state fluctuations in pupil size) in 3 to 6-month-old infants and pre-presbyopic adults. Accommodative microfluctuations of infants are about two to three times larger than those of adults (Candy & Bharadwaj, 2007) but pupillary hippus has not been characterized during visual development. Steady-state temporal fluctuations in retinal image quality occurring due to accommodative microfluctuations and pupillary hippus could influence both optical and neural development (Mitchell & Timney, 1984; Wildsoet, 1997; Winawer & Wallman, 2002). In adults, the accommodative microfluctuations can be up to 0.15 D RMS, with a bandwidth of up to 3 Hz (Charman & Heron, 1988) while pupillary hippus can extend up to 1 mm RMS in diameter, with a bandwidth ranging from 0.75 to 2.5 Hz (Bouma & Baghuis, 1971; McLaren, Erie, & Brubaker, 1992; Stark, Campbell, & Atwood, 1958).

Overall, this study characterized three fundamental components of pupillary responses that help determine retinal image quality in the typically developing visual system: i) responses to binocular and monocular changes in near visual demands ii) sensitivity to small sinusoidal changes in demand and iii) stability of steady-state responses.

Methods

Subjects

Typically developing infants and children were recruited from local birth records and pre-presbyopic adults, with no reported ocular or medical conditions, were recruited from the local academic department. The subjects were initially recruited to participate in a number of studies of accommodation and vergence (Bharadwaj & Candy, 2008; Candy & Bharadwaj, 2007; Wang & Candy, 2010), but pupil responses were collected simultaneously by the photorefractor system and these data are now summarized here. Infants and children were born within 3 weeks of their due date and were expected to be typically hyperopic (Mayer, Hansen, Moore, Kim, & Fulton, 2001). They did not wear any refractive correction during the experiment, to maintain their daily natural viewing conditions, which may have resulted in an unknown amount of accommodative miosis in their effort to focus on near targets. The data reported here therefore address the habitual responses of uncorrected infants in their typical environment. Adults were near emmetropic (low amounts of hyperopia or up to 1.0 D of myopia) and wore their habitual correction during the experiment (soft contact lenses only). The studies adhered to the tenets of the Declaration of Helsinki and were conducted after approval by Indiana University's local Institutional Review Board with the informed consent of the adult subjects and parents of the infants and children.

Procedure and data analysis

Pupil, accommodation and gaze responses of each eye were measured simultaneously at 25 Hz using the Power-Refractor (PR) [Multi Channel Systems, Reutlingen, Germany] (Choi et al., 2000; Schaeffel et al., 1993). Subjects were aligned at 1.0 m from a set of LEDs immediately beneath a camera aperture. Light from the LEDs passed into the eye and was reflected back from the retina through the pupil. Vertical and horizontal pupil diameters

were measured (in millimeters) using the PR's edge-detection algorithm and they were averaged to give the overall pupil diameter (Schaeffel et al., 1993). The accommodative state of the eye (in diopters) was derived in the vertical meridian from the slope of a linear regression fit to the distribution of reflected light across the pupil. Horizontal gaze positions were determined (in degrees) from the relative displacement of the first Purkinje image with respect to the center of the pupil image (Riddell, Hainline, & Abramov, 1994) and vergence (in prism diopters) was calculated as the difference in horizontal gaze position between the two pupillary axes. These units were converted into meter angles (MA, m^{-1}), to compensate for age-related changes in inter-pupillary distance (IPD) (MacLachlan & Howland, 2002). An IPD of 61 mm was used for adults.

Subjects watched a high-contrast cartoon image or a movie on an LCD display (2.3° by 2.3° at 50 cm) that was reflected from a beamsplitter (Figure 1). The visual target was presented at a mean luminance of approximately 4 cd/m^2 in a dark surround to ensure that the pupil diameters were within the operating range of the PR (3 mm to 8 mm). The screen and beamsplitter were mounted on a motorized track that moved them in real space. The subject was carefully aligned so that the target movement was centered on the midline between their eyes. An experimenter gently supported each infant or young child's chin, to keep them aligned and to minimize head movements. Older children and adults were instructed to hold their heads as stable as possible. No specific instructions were given to the older children and adults regarding the task—they were merely asked to watch the target (Stark & Atchison, 1994).

The three experimental protocols were as follows:

Experiment I determined the characteristics of pupil responses to gradual ramp changes in near visual demand. Data from 60 subjects [twenty infants (2.8–9.9 months), twenty children (2.1–3.9 yrs) and twenty adults (18.1–41.1 yrs)] were included in the analyses. The subjects tracked the LCD screen as it moved eight times between 80 and 33 cm (1.75 D or MA) at one of three different speeds (0.25, 0.50 and 0.75 D/s), with a stable period of 4 s at each viewing distance (see stimulus trace in Figure 2). In the binocular condition, subjects watched the target with both eyes and all cues (including blur, disparity and proximity) were available and consistent with each other to drive the near response. In the monocular condition, the subject's right eye was occluded using a $75 \text{ mm} \times 75 \text{ mm}$ Kodak Wratten #87 infrared transmitting filter, such that PR images were collected from both eyes even though viewing was monocular. Multiple speeds were used again in this condition to minimize the potential for predictive responses (Stark, 1968; van der Wildt, Bouman, & van de Kraats, 1974) and all three speeds have been shown to elicit only ramp accommodative (Hung & Ciuffreda, 1988) and vergence (Semmlow, Hung, & Ciuffreda, 1986) responses in adults. No systematic difference in performance was noted across different speeds and therefore the three sets of responses were pooled in analyses.

The raw stimulus, pupil diameter, accommodation and gaze position data were all smoothed using a 200 ms running-average window to maintain the temporal relationship between them. The stimulus profile was divided into epochs, each containing a 4 s stable stimulus period plus the change in stimulus before and after this period (Figure 2) (Bharadwaj & Candy, 2008). The final pupil, accommodation and vergence responses were obtained by averaging 2 s (50 data points) of the stable portion of each usable epoch. The change in pupil diameter (Δpd), accommodation (Δacc) and vergence ($\Delta verg$) with viewing distance was then calculated as the difference in response states at the 80 and 33 cm viewing distances. If a subject provided multiple responses in each condition, the responses were averaged to obtain the overall mean pupil diameter, accommodation and vergence.

Responses in each epoch were included in the analyses only if they met the following criteria:

1. Accommodation data were within the linear operating range of the instrument (+4.0 to -6.0 D) and the pupil diameters were between 3 and 8 mm (required for the instrument to collect data) (Choi et al., 2000; Schaeffel et al., 1993).
2. The data were collected from a gaze eccentricity of less than 15° from the pupillary axis to minimize the impact of peripheral refraction on accommodation estimates (Jennings & Charman, 1981; Navarro, Artal, & Williams, 1993). Subjects typically maintained stable gaze on the target, and so very little data were excluded as a result of this criterion.
3. The correlation between stimulus and left gaze position (irrespective of what the right eye was doing) in a given epoch was > 0.7 , suggesting that the near-motor responses represented a valid attempt to follow the target position (Bharadwaj & Candy, 2008). Response epochs with correlations between 0.6 and 0.7 were visually inspected and included in the analyses only if the left gaze position appeared to systematically track the movement of the stimulus (Bharadwaj & Candy, 2008).

Experiment II measured the threshold near-visual demand that would elicit a reliable pupillary response in 41 subjects (33 2 to 4-month-olds and 8 adults) under binocular and monocular viewing conditions (the right eye was occluded using the Wratten IR filter). The stimulus moved quasi-sinusoidally in diopters before the subjects at a temporal frequency of 0.1 Hz, for 30 sec, with amplitudes of 0.25 D (or MA), 0.5 D (or MA) and 0.75 D (or MA), around a baseline distance of 2 D (or MA) [i.e. 50 cm from the subject] (Figure 5 panel a). The baseline distance of 2 D was chosen to center the stimulus in a typical range for infant activities. Each stimulus amplitude was presented for three cycles, with the 0.5 D amplitude presented first, the 0.25 D amplitude presented next and the 0.75 D amplitude presented last. An unpredictable aperiodic stimulus movement was also inserted between amplitudes to disturb any predictive responses (Figure 5 panel a). This temporal frequency is in the range where the pupillary light responses of adults show the maximum gain (Sherman & Stark, 1957). Ten infants and six adults also viewed the target binocularly at a constant viewing distance of 50 cms for 30 s to confirm that the pupils do not show a response at 0.1 Hz in the absence of the stimulus. Any response at 0.1 Hz in this condition was considered to be noise in the calculation of a significant signal-to-noise ratio (described below).

No smoothing procedure was applied to these raw data. Data were included in the analyses only if they met the first two inclusion criteria of Experiment I and if the total number of missing data points for one sinusoidal amplitude level was less than one-third of the total number of possible data points that could be recorded (i.e. $25 \text{ fps} \times 30 \text{ s} / 3 = 250$ data points) (Wang & Candy, 2010). Missing data could be the result of blinks or periods of fussiness or inattention. The pupillary responses to sinusoidal stimulation were analyzed in the manner described by Wang and Candy (2010) for accommodation data. Briefly, a Fourier transform was applied to the stimulus and pupil responses to compute their amplitude spectra. The overall goal of the analysis was to determine the stimulus amplitude at which the pupillary response at 0.1 Hz was significantly different from the responses at other frequencies, indicating that the pupils responded to the target motion. The response at 0.1 Hz was treated as the signal and responses at the adjacent frequencies (0.067 Hz and 0.133 Hz) were used to estimate the noise. Only data from the left eye will be reported here.

The criterion for a significant signal-to-noise ratio (SNR) was developed for these data using the approach used by Wang and Candy (2010) for the accommodation data. A Fourier transform was applied to the pupil data for the static target and an SNR for each subject was

calculated. SNR data from one infant and one adult were rejected because their data were greater than $3SD$'s away from the mean SNR for that age group. The mean ($\pm SD$) $\log(\text{SNR})$ of the left eye's pupil response at 0.1 Hz in the absence of the sinusoidal stimulus was -0.16 (± 0.21) for infants and -0.13 (± 0.25) for adults. Assuming the $\log(\text{SNR})$ is normally distributed, a one-tailed 95% confidence interval provides an SNR criterion of 1.56 for infants [i.e. $-0.16 + 1.65 * 0.21 = 0.19$; $10^{0.19} = 1.56$] and 1.94 for adults [i.e. $-0.13 + 1.65 * 0.25 = 0.29$; $10^{0.29} = 1.94$]. Therefore, pupillary responses at 0.1 Hz for the sinusoidal stimuli with an SNR 1.56 for infants and 1.94 for adults were considered significant.

Experiment III determined the stability of steady-state pupil responses under binocular viewing conditions for eight infants (3.1–6.2 months) and eight adults (18.3–41.4 yrs). Subjects watched the stimulus at a constant viewing distance of 80 cms for 14 s. The first 10.24 s of stable recording (yielding 256 [2⁸] data points) from the right eye of each subject was analyzed if the data met the first two inclusion criteria from Experiment I and if there were no more than eight consecutive data points (320 ms) missing in a given 10.24 s of stable recording (Candy & Bharadwaj, 2007). Missing data of less than eight consecutive points were interpolated using a cubic spline algorithm (Collins, Davis, & Wood, 1995). If a subject generated more than one usable recording, the first recording was included in the analyses. Stability of the steady-state pupil response was determined by computing the root-mean-square (RMS) fluctuation (time-domain analysis) (Daum & Fry, 1982) and by computing the amplitude spectrum using Fourier analysis (frequency-domain analysis) (Bouma & Baghuis, 1971; Stark & Baker, 1959; Stark et al., 1958). The frequency bandwidth available for analysis ranged from 0.09 Hz (fundamental frequency) to 12.5 Hz (Nyquist limit for a 25 Hz recording). The individual subjects' amplitude spectra were averaged within each age group to obtain the mean amplitude spectrum for infants and adults.

Results

Experiment I. Pupil responses to binocular and monocular ramp stimuli

Figure 2 plots representative pupil, accommodation and vergence responses to ramp stimuli for an infant (panels a and b) and adult (panels c and d) under the binocular (left panels) and monocular (right panels) viewing conditions. For all three age groups, the accommodative, vergence and pupil responses generated under binocular conditions were more robust than their monocular counterparts. The pupil responses of a number of infants, children and adults to an increase in near-visual demand were sometimes transient (approximately 15% of all responses) even though the corresponding accommodative and vergence responses were sustained (closed arrowheads in Figure 2). The pupil diameter of these subjects reduced transiently as the stimulus moved from 80 to 33 cms and returned to the baseline dilated state, while the stimulus remained at 33 cm.

The mean ($\pm 1 SD$) left eye pupil diameter at 80 cms was similar for all three age groups under binocular (infants 5.43 ± 0.61 mm; children: 5.57 ± 0.8 mm; adults: 5.7 ± 0.85 mm) and monocular (infants: 5.69 ± 0.59 mm; children: 5.72 ± 0.81 mm; adults: 5.79 ± 0.78 mm) viewing conditions. The change in pupil diameter with viewing distance (Δpd) was matched in the two eyes for all age groups under both viewing conditions. The difference in Δpd between the eyes was distributed around zero in both viewing conditions, with a mean difference of 0.001 mm (95% CI: ± 0.21 mm) under binocular conditions and -0.003 ± 0.21 mm under monocular conditions (Figure 3). There was no trend for the difference in Δpd between the eyes to change as a function of the mean Δpd (Figure 3).

Large inter-subject variability in Δpd was observed in all three age-groups, more for adults than infants and children, and more under binocular than monocular conditions. Figure 4 shows the mean ($\pm 1 SD$) and individual Δpd (panels a and b), Δacc (panels c and d) and $\Delta verg$ (panels e and f) for all three age groups under binocular and monocular viewing conditions. Separate 2-factor ANOVA's (age \times viewing condition) were performed on the left eye Δpd , left eye Δacc , and $\Delta verg$. The details are shown in Table 1. Overall, the mean Δpd , Δacc and $\Delta verg$ were statistically significantly higher under binocular than under monocular conditions ($p < 0.001$ for all). The mean Δpd of infants and children were statistically significantly smaller than that of adults (both $p < 0.01$) but not significantly different from each other ($p = 0.11$). The main effect of age was not statistically significant for Δacc or $\Delta verg$ ($p > 0.09$ for both) while the interactions between age and viewing condition were statistically significant for both Δacc and $\Delta verg$ ($p < 0.01$). There was poor correlation between the Δpd , Δacc and $\Delta verg$ for all three age groups in both viewing conditions ($r < 0.3$ or > -0.3 and $p > 0.5$ for all correlations).

The monocular to binocular Δpd , Δacc and $\Delta verg$ ratios (mono/binocular ratio) were computed to determine whether the relative reduction in response in monocular viewing was consistent throughout the near triad. The infant and child mono/binocular ratios were similar for all three ratio types and they were smaller than those of adults (Table 2). The adult mono/binocular ratio for Δpd and Δacc were similar to each other and larger than $\Delta verg$ (Table 2). A 2-factor ANOVA (ratio type \times age) showed a statistically significant main effect of age [$F(2, 152) = 4.99$; $p = 0.008$] but not of ratio type [$F(2, 152) = 1.57$; $p = 0.21$] or interaction between age and ratio type [$F(4, 152) = 0.87$; $p = 0.49$]. A post-hoc Games–Howell test confirmed that the mono/binocular ratios of infants and children were statistically significantly smaller than those of adults (both $p < 0.05$) but not significantly different from each other ($p = 0.78$). This result indicates that the relative reduction in monocular response magnitude was similar for all three components of the near-triad, with the reduction being larger in infants and children than in adults. The smaller mono–binocular ratio of $\Delta verg$ in adults than Δacc was expected given that the AC/A ratio in meter angles is typically less than unity (around 0.6–0.8 MA/D) (Bharadwaj & Candy, 2008; Fincham & Walton, 1957; Morgan, 1968). The mean monocular vergence to accommodation ratio (i.e. the response AC/A ratio) of infants (1.15 MA/D), children (0.85 MA/D) and adults (0.72 MA/D) obtained in this experiment were similar to those obtained in previous literature (Bharadwaj & Candy, 2008; Turner et al., 2002).

Pupil responses to light tend to increase with initial pupil diameter in adults and children (Loewenfeld, 1993b). Correlations between left eye Δpd and pupil size at the 80 and 33 cm viewing distances were calculated to determine if a similar relationship exists for the near response. The correlation between Δpd and pupil diameter at 80 cm was poor and statistically insignificant for all ages and both viewing conditions. Binocular Δpd was significantly negatively correlated with pupil diameter at 33 cm for adults only ($r = -0.59$; $p < 0.001$), and not for infants or children (both $r = -0.13$; $p = 0.67$). Monocular Δpd was significantly negatively correlated with pupil diameter at 33 cm for all three age groups (infants $r = -0.38$; $p = 0.02$; children $r = -0.39$; $p = 0.02$; adults $r = -0.68$; $p < 0.001$). Overall, it seems logical that the size at 33 cm was negatively correlated with Δpd given that the pupil size at 80 cm was similar across subjects. In other words, the change defines the end-point of the pupillary miosis response.

Experiment II. Pupil responses to sinusoidal changes in near-visual demand

Figure 5 panel a shows representative raw traces of pupil responses to the quasi-sinusoidal stimulus from an infant and an adult under binocular viewing conditions. The pupil responses to the 0.25 D and 0.50 D stimulus appeared minimal while the responses to the

0.75 D stimulus appeared significant. Monocular pupil responses of adults were similar to those of the binocular viewing condition while there was no apparent response even to the 0.75 D stimulus in infants. Figure 5, panels b–e show the pooled amplitude spectra of infants (panels b and d) and adults (panels c and e) for the three quasi-sinusoidal stimuli under binocular (panels b and c) and monocular (panels d and e) viewing conditions, with histograms of the mean (± 1 SD) response amplitude at 0.1 Hz (panel f). A 3-factor ANOVA was performed to determine the effect of age, stimulus amplitude and viewing condition on the response amplitude at 0.1 Hz, and the details of this analysis are shown in Table 3. Overall, the response amplitude was larger under binocular than monocular conditions ($p < 0.001$), larger for adults than for infants ($p < 0.001$), and larger for 0.75 D than 0.25 D and 0.50 D stimuli ($p < 0.001$) (Figure 5, panel f; Table 3). The response amplitudes for 0.25 D and 0.50 D were not statistically significantly different from each other ($p = 0.25$) (Table 3). The interaction between age and stimulus amplitude was also statistically significant ($p < 0.001$) while the other interactions were not for this sample size (Table 3). The response amplitudes at other frequencies (that were not related to the stimulus) did not show any stimulus dependent change (Figure 5, panels b–e).

Figure 5, panel g plots the mean (± 1 SD) SNR of infants and adults for the three stimulus amplitudes under binocular and monocular viewing conditions. Under binocular conditions, the mean SNR of infants and adults reached their threshold significance, values of 1.56 and 1.94, respectively, only for the 0.75 D stimulus (Figure 5, panel g). Under monocular conditions, the mean infant SNR did not reach the threshold for any of the three stimuli and the adult SNR reached threshold only for the 0.75 D stimulus (Figure 5, panel g). Large inter-subject variability in the SNR was observed, and although the mean binocular SNR of the 0.25 D and 0.5 D stimuli did not reach the threshold value, the SNR of 10 (out of 33) and 13 (out of 33) infants did reach the threshold value, respectively. Under monocular conditions, the SNR of 5 (out of 27), 7 (out of 27) and 10 (out of 27) infants reached the threshold value, for the 0.25, 0.5 and 0.75 stimuli respectively, although the mean SNR was below the threshold for all three stimuli. In adults, the binocular SNR's reached the threshold value in 2 (out of 10) and 5 (out of 10) subjects for the 0.25 D and 0.5 D stimuli, respectively, and the monocular SNR's reached the threshold value in 1 (out of 10) and 3 (out of 10) subjects for the same two stimuli respectively.

Experiment III. Stability of steady-state pupil responses

The mean (± 1 SD) binocular pupil diameter of infants (5.35 ± 0.67 mm) and adults (6.23 ± 1.08 mm) were not statistically significantly different from each other ($p = 0.12$). A one-way ANOVA (with post-hoc Games–Howell test) showed that the RMS deviations of infants (mean ± 1 SD: 0.12 mm ± 0.05 mm) and adults (0.16 ± 0.06 mm) were also not significantly different from each other ($p = 0.24$), but they were significantly different from a model eye (0.03 mm ± 0.006 mm) ($p < 0.001$) (Figure 6, panel a). The amplitude spectra of both infants and adults show a gradual reduction in amplitude with increasing temporal frequency until they reach the level of the model eye by 3.5 Hz (Figure 6, panels b–d). There was little difference in the amplitude spectra of the infants and adults, except for the lower-most temporal frequencies (Figure 6, panel d). Overall, these results indicate that the pupil responses demonstrated small fluctuations during viewing of a stable visual target.

Discussion

Summary of results

- a. Pupil diameter of 3 to 9-month-old infants, 2 to 4-yr-old children and adults changed equally (within 0.2 mm of each other) in the two eyes with viewing distance (Figure 3).

- b. Pupil responses to a ramp increase in near-demand showed a transient constriction followed by a re-dilation in approximately 15% of the subjects across all age groups (Figure 2).
- c. The mean Δpd was smaller in infants and children than adults (Figures 2 and 4), albeit with large inter-subject variability in all three age groups (Figure 4).
- d. The mean Δpd was larger under binocular than under monocular conditions for all age groups (Figures 2 and 4). This result is similar to the smaller monocular accommodation and vergence responses when compared to binocular conditions (Figure 4).
- e. The relationship between Δpd and pupil diameter suggested that the size at 33 cm was defined by the Δpd change for this light level.
- f. The pupils of 3 to 4-month-olds responded significantly to a 0.75 D quasi-sinusoidal stimulus (modulating at 0.1 Hz) under binocular conditions, but not under monocular conditions (Figure 5). Adult pupils responded to the 0.75 D sinusoidal stimulus under both viewing conditions.
- g. Steady-state fluctuations in pupil diameter were similar in infants and adults, with the fluctuations being slightly larger in infants than adults at low temporal frequencies (Figure 6).

Target luminance and the near response

The mean luminance of the visual stimulus used in this experiment (4 cd/m^2) was somewhat lower than previous investigations of the pupillary near reflex [e.g. 30 cd/m^2 in Schaeffel et al. (1993), 5 and 100 cd/m^2 in Gislen et al. (2008) and 10 cd/m^2 in Kasthurirangan and Glasser (2006)]. The low luminance ensured that the pupil diameters were within the operating range of the Power-Refractor (3 mm to 8 mm). The target was, however, presented against a dark surround, at high contrast and with a similar spatial amplitude spectrum to naturalistic stimuli (Tolhurst, Tadmor, & Chao, 1992). Binocular accommodative and vergence responses when viewing this target moving in depth had gains that were appropriate to the stimulus demand, indicating that the visual target acted as a strong stimulus for the near-response despite its low luminance. Further, Gislen et al. (2008) did not observe any difference in the pattern of near-pupil responses in children and adults for their 5 and 100 cd/m^2 luminance levels.

The transient pupil responses seen in this experiment are similar to those seen in adults for a step increase in light level (Lowenstein & Loewenfeld, 1959; Sun & Stark, 1983; Sun, Tauchi, & Stark, 1983) and for a monocular step increase in the near-visual demand (Kasthurirangan & Glasser, 2006). The transient responses tend to become more sustained when the stimulus brightness (Lowenstein & Loewenfeld, 1959; Sun & Stark, 1983; Sun et al., 1983) or the near-visual demand is increased (Kasthurirangan & Glasser, 2006).

Pupil response and retinal image quality at near

The pupil impacts retinal image quality by reducing the influence of optical aberrations (Charman, 1991; Liang & Williams, 1997) and changing the optical depth-of-focus (DOF) (Charman & Whitefoot, 1977; Ward & Charman, 1985, 1987). In this study, pupil diameter decreased with a ramp increase in near-visual demand, less so for infants and children than for adults for the same baseline pupil size (Figure 4, panels a and b). This is consistent with the data from step changes in near-visual demand from older children (Gislen et al., 2008; Schaeffel et al., 1993; Wilhelm et al., 1993) and suggests that the pupils of the typically developing infants and children may contribute less towards the maintenance of retinal image quality at near than in adults. The impact of individual differences in the near

response may be significant, given the relatively large variability in response. The RMS deviations of steady-state pupil diameter were similar for infants and adults (Figure 6, panel a), suggesting that any temporal variability in retinal image quality from these fluctuations is likely to be similar in the two age groups.

The optical DOF changes nonlinearly with pupil size—it increases dramatically for pupil diameters smaller than 3 mm while it remains relatively constant for sizes greater than 3 mm (Charman & Whitefoot, 1977). The slope of the accommodative stimulus–response function also starts to decrease for pupil diameters smaller than 1.5 mm, reaching a near-zero slope by 0.5 mm (i.e. blur open-loop conditions) (Ward & Charman, 1985, 1987). In this study, pupil diameters across all age groups and viewing conditions ranged from 4 mm to 7 mm (Figure 3), suggesting that changes in the optical DOF would have been minimal. The primary onus of achieving and maintaining clear retinal image quality at near therefore appears to lie with the accommodative system during slow tracking of a visual stimulus at these light levels.

Why might the near-pupillary response of infants and children be smaller than that of adults?

Four possible explanations are considered here.

First, the magnitude of the responses might be related to the baseline pupil diameter, as pupillary responses of adults and children to short pulses of light tend to be greater for larger baseline pupil diameters (Loewenfeld, 1993b). The baseline pupil diameter here at an 80 cm viewing distance was similar as a function of age and it was poorly correlated with the magnitude of pupillary miosis. These results are similar to those observed by Wilhelm et al. (1993). In fact, when taking into account the smaller size of the immature eye, the baseline pupil size at 80 cm viewing distance is proportionally larger in the younger groups, and yet their responses were smaller.

Second, the increased Δpd of adults when compared to infants and children could be related to the neural effort expended to generate the near accommodative response with an age-related reduction in the compliance of the crystalline lens (Atchison, 1995; Fincham, 1951; Schor & Bharadwaj, 2005). Increased neural effort to mold an aging crystalline lens is suggested by an increase in the response AC/A ratio and a decrease in the response CA/C ratio within the linear range of the accommodative stimulus–response function (Fincham, 1951). However, in contradiction to the expected increase in near-pupillary constriction, Kasthurirangan and Glasser (2006) observed no change or even a slight reduction in the magnitude of monocular near-pupillary constriction between 14 and 45-yr-old subjects—an age range over which there is a dramatic reduction in the compliance of the crystalline lens (Schor, Bharadwaj, & Burns, 2007; Weeber et al., 2005). This suggests that differences in neural effort to achieve the accommodative response may contribute only little to the increased Δpd of adults.

Third, the reduced Δpd could be due to functional immaturity of the iris plant (consisting of the sphincter and dilator muscles) that regulates the size of the pupil. This possibility seems unlikely because the iris muscles are functionally mature at birth (Loewenfeld, 1993b) and the pupillary responses of infants and children to a step change in light level are similar (Birch & Held, 1983) [or only marginally smaller (Loewenfeld, 1993b)] to those of pre-presbyopic adults. The pupils of premature infants can also dilate up to 90% of their corneal diameter when treated with pharmacological agents—this dilation is more than is seen in older children or adults (Carpel & Kalina, 1973). This hypothesis therefore does not appear to account for the age-related differences in Δpd either (Loewenfeld, 1993b).

Fourth, the reduced Δpd of infants and children may reflect an immaturity in the neural input from the midbrain near-response cells to the corresponding muscles (sphincter and dilator for the pupil, ciliary muscle for accommodation and medial and lateral recti for vergence). This possibility seems unlikely for two reasons. One, the binocular accommodative and vergence responses of infants and children are similar to those of adults (Figure 4, panels c and e), indicating that these two components of the near-triad can exhibit almost adult-like behavior (Banks, 1980; Bharadwaj & Candy, 2008; Turner et al., 2002). Two, neural coupling between the components of the near-triad also appears to be functioning within the first few months of life. The coupling between accommodation and vergence (as determined by the response AC/A and CA/C ratios) becomes adult-like within the first few years of life (Bharadwaj & Candy, 2008; Bobier, Guinta, Kurtz, & Howland, 2000; Turner et al., 2002). In this study, the mean response AC/A ratio was 1.15 MA/D for infants, 0.85 MA/D for children and 0.72 MA/D for adults and they were similar to those obtained in previous literature (Bharadwaj & Candy, 2008; Turner et al., 2002). The mean ratio of monocular Δpd to monocular Δacc of infants (0.26 mm/D) was smaller than those of children (0.45 mm/D) and adults (0.45 mm/D) who participated in this study (compare panels b and d in Figure 4), suggesting that, at a population level, the coupling between accommodation and pupil responses may be somewhat weaker in 3 to 9-month-old infants than in 2 to 4-yr-old children and adults. Monocular pupil responses of infants were similar to those of children and they were significantly smaller than those of adults (Figure 4, panel b), indicating that the strength of coupling between pupils and accommodation may contribute little towards the reduction in monocular pupillary responses. The coupling between vergence and pupil responses was not determined in this study because vergence responses were not measured under blur-open loop conditions.

The relatively simple candidate explanations listed above do not provide a single compelling explanation for reduced miosis during near responses in infants and children. Overall, as suggested by Wilhelm et al. (1993), some combination of reduced innervation to the pupil and/or reduced mechanical response to the innervation appears responsible for reduced pupillary near-response during typical visual development. From a clinical standpoint, the reduced near-pupillary responses in infants and children suggests that the visual target might need to be taken very close to the infant/child to observe near-pupillary miosis.

Performance of the near-triad under binocular and monocular viewing conditions

Monocular Δpd , Δacc and $\Delta verg$ to ramp changes in near-visual demands were significantly smaller than their binocular counterparts for all three age groups, with infants and children showing a greater reduction in performance than adults (Table 2). For adults, vergence responses showed a larger reduction in monocular performance than accommodation and pupils, although this difference was not statistically significant (Figures 2 and 4, Table 2). Smaller mono–bino ratio of $\Delta verg$ in adults than Δacc was expected given that the AC/A ratio in meter angles is typically around 0.6–0.8 MA/D (Bharadwaj & Candy, 2008; Fincham & Walton, 1957; Morgan, 1968). Monocular pupil responses of infants to sinusoidal stimuli were also smaller than binocular responses in Experiment II (Figure 5). These results indicate that monocular cues (e.g. retinal blur and sense of proximity) alone are less efficient at driving the near-pupillary response and that they are supplemented by binocular cues (e.g. retinal disparity, binocular summation of input from the two eyes) to generate larger responses. The current experiment measured near-pupil responses only under disparity feedback open-loop conditions and not under blur feedback open-loop conditions. The relative contribution of the different binocular and monocular sensory cues in driving near-pupillary responses therefore remains to be determined.

The overall pattern of results is similar to the accommodative and vergence responses from infants and children (Bharadwaj & Candy, 2008; Turner et al., 2002) and extends the result

to the pupil response. The pupil response to light in human infants (Birch & Held, 1983; Sireteanu, 1987), adults (Kurz, Krummenauer, Pfeiffer, & Dick, 2004; ten Doesschate & Alpern, 1967) and rhesus monkeys (Clarke, Zhang, & Gamlin, 2003) is also smaller under monocular conditions than under binocular conditions. In humans, the difference between monocular and binocular light responses appears around the onset of responses to disparity (Birch & Held, 1983). Overall, these results demonstrate the role of binocular information in driving all components of the near-triad, more so during visual development than adulthood. The adult data in this study are in conflict with those of Marg and Morgan (1949), who observed no significant difference in the magnitude of binocular and monocular pupillary responses to changes in target distance. One reason for this difference might be that naive subjects with minimal instruction were used in the current study. All of Marg and Morgan's subjects were given a number of weeks of practice with the task before the actual experiment. In support of this hypothesis, accommodative responses are significantly smaller in monocular viewing than binocular viewing in naïve, uninstructed adults (Horwood, Turner, Houston, & Riddell, 2001) but not in more experienced subjects (Ramsdale, 1979).

Conclusions

Near-pupil responses of typically developing 3 to 9-month-old infants and 2 to 4-yr-old children are matched in the two eyes (within 0.2 mm), are typically generated to more than 0.5 D of change in near visual demand, and have steady-state fluctuations similar to those of adults. Smaller changes in pupil diameter of infants and children with viewing distance indicates that the developing pupil system may contribute less towards improving retinal image quality for slow moving objects than for adults. Similar reduction in monocular pupil, accommodation and vergence responses indicates an overall reduction in performance of the near-triad upon removal of binocular cues. Conversely, these results reflect the role of binocular cues in driving all three components of the near-triad during typical visual development.

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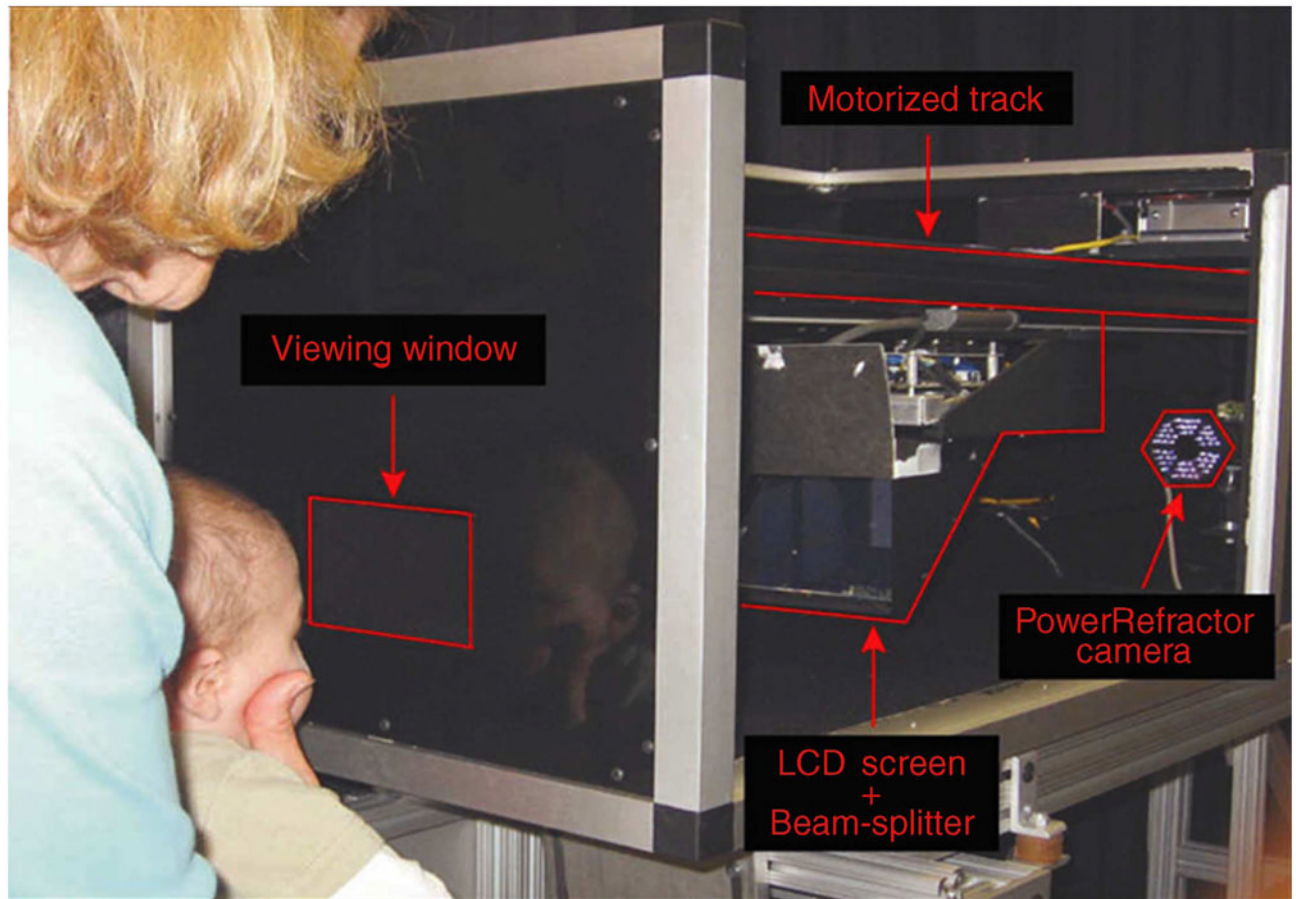


Figure 1.

The experimental equipment with its key elements highlighted. The visual target was displayed on the LCD screen and presented via a beamsplitter to the subject. The screen and beamsplitter were mounted on a motorized track that could be moved in real space to change the near-visual demand. The screen and beamsplitter ramped towards and away from the subject in Experiment I, moved sinusoidally in Experiment II and remained stationary at 80 cm in Experiment III.

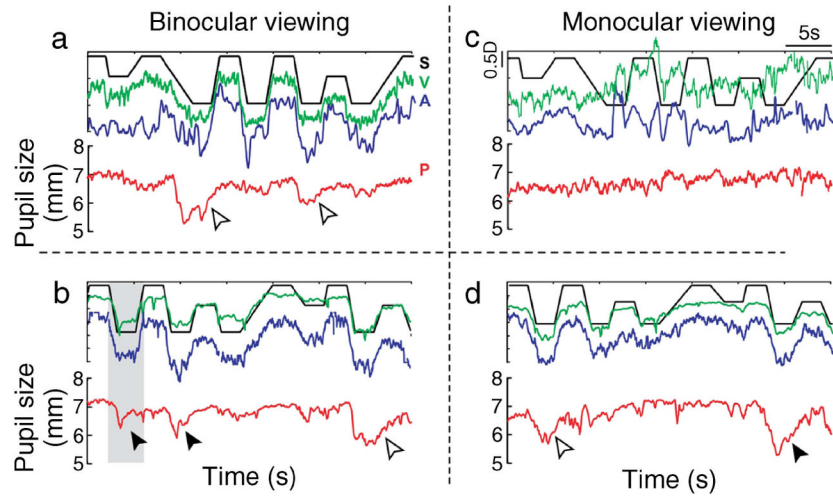


Figure 2. Raw stimulus (S), accommodation (A), vergence (V) and pupil (P) traces plotted as a function of time for a representative 5.6-month-old infant (panels a and c) and 26.2-yr-old adult (panels b and d) under binocular (panels a and b) and monocular (panels c and d) viewing conditions in Experiment I. The stimulus, accommodation and vergence traces are shifted vertically for clarity (scaling shown in top right panel). The horizontal relationship between these three traces is not altered. Pupil traces are plotted on an absolute scale. The gray box in the bottom left panel shows a representative epoch used for calculating the correlation between gaze and stimulus position.

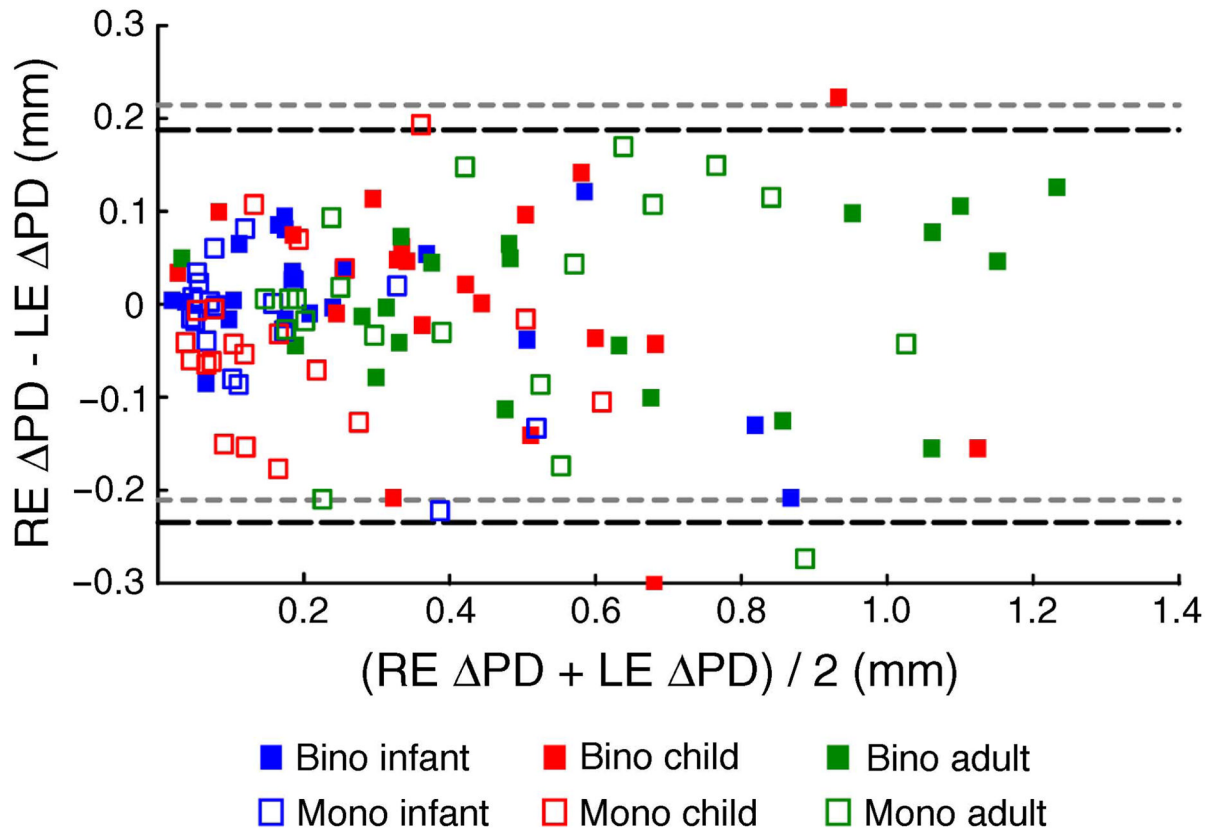


Figure 3.

The difference between right and left eye Δpd plotted as a function of the mean Δpd under binocular (closed symbols) and monocular (open symbols) viewing conditions in Experiment I. The black and gray dashed lines indicate 95% CI's about the mean Δpd for all ages combined under binocular and monocular conditions, respectively. The pupil diameter of 3 to 9-month-old infants, 2 to 4-yr-old children and adults changed equally with viewing distance in the two eyes (within 0.2 mm of each other), for both viewing conditions.

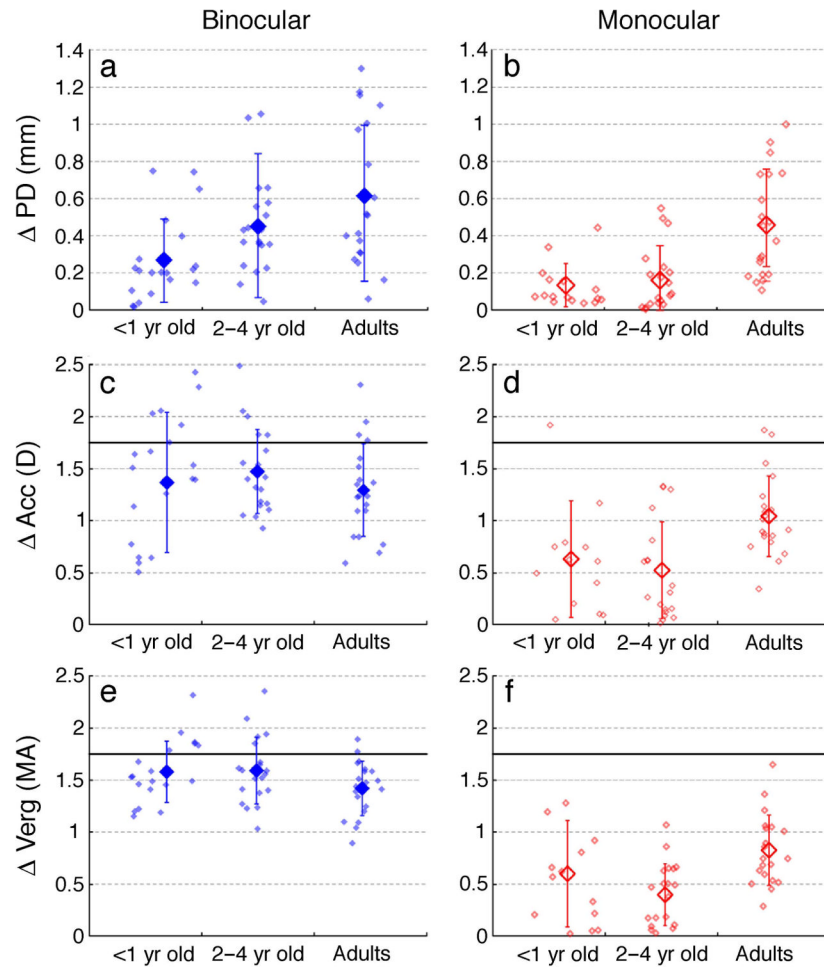


Figure 4.

Δpd (panels a and b), ΔAcc (panels c and d) and $\Delta Verg$ (panels e and f) for each age group under binocular (left panels) and monocular (right panels) viewing conditions in Experiment I. The small diamonds in all panels show data from individual subjects and the big diamonds represent the mean data. Error bars show $\pm 1 SD$. The horizontal spread in the small diamonds in each panel indicate that subjects of different ages were present within a given age group. The big diamonds represent the average data of all these ages within a given group. The mean pupil, accommodative and vergence responses to the ramp stimuli were larger under binocular than under monocular conditions, albeit with large inter-subject variability. The monocular pupil, accommodative and vergence responses of adults were also larger than those of infants and children.

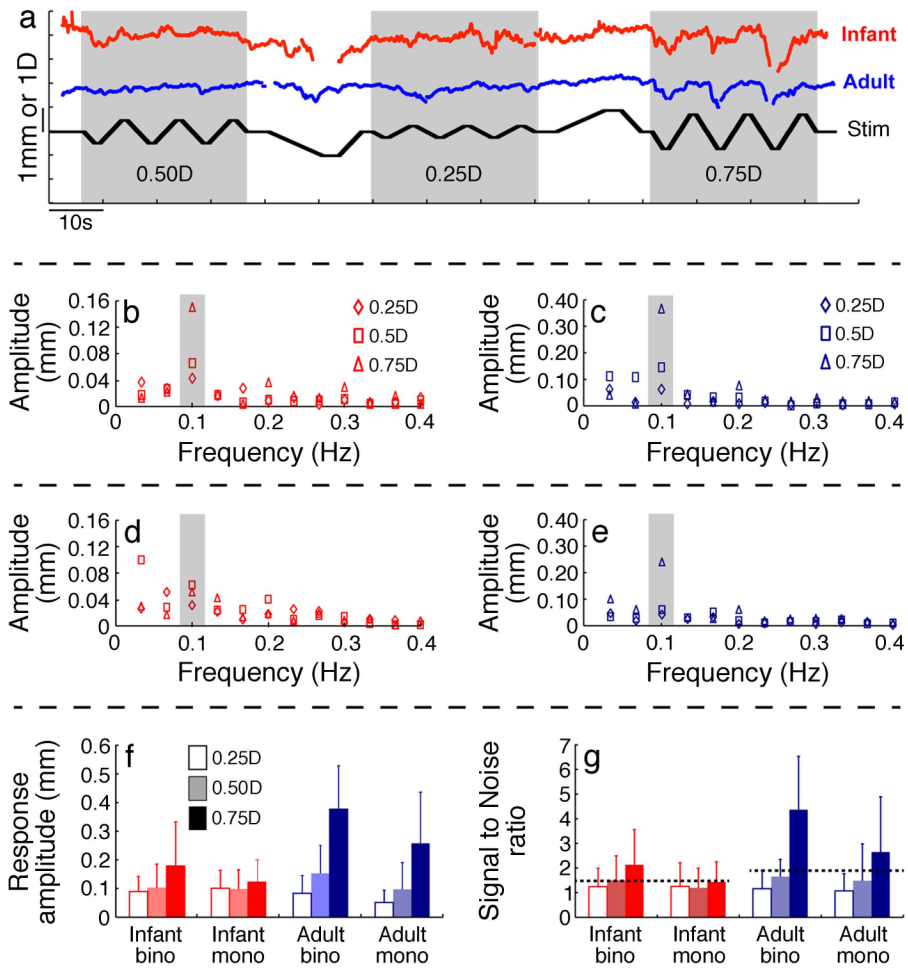


Figure 5.

Panel a: Representative raw traces of pupil responses of an infant and adult to the quasi-sinusoidal stimulus used in Experiment II plotted as a function of time under binocular viewing conditions. The stimulus and pupil response traces are shifted vertically for clarity (scaling shown in top right panel). The horizontal relationship between the traces is not altered. Panels b–e: Amplitude spectra of infant (panels b and d) and adult (panels c and e) pupil responses under binocular (panels b and c) and monocular (panels d and e) viewing conditions. In panels b–e, the pupil responses from individual subjects were pooled together and the Fourier transform of the pooled data is shown to demonstrate the overall trend. The gray bars in panels b–e highlight the response amplitude to the 0.1 Hz stimulus frequency. Note that the ordinate scales of panels c and e are different than those of panels b and d. Panel f: Mean (± 1 SD) binocular and monocular pupillary response amplitude at 0.1 Hz. Panel g: Mean (± 1 SD) binocular and monocular SNR's of infants and adults at 0.1 Hz. The dashed lines indicate the threshold SNR calculated when the target was stationary. The pupils of 3–4 month-olds responded significantly to a 0.75 D quasi-sinusoidal stimulus under binocular conditions, but not under monocular conditions. Adult pupils responded to the 0.75 D sinusoidal stimulus under both viewing conditions.

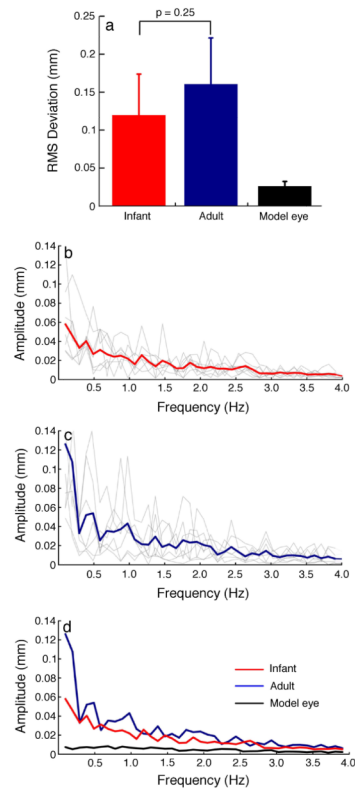


Figure 6.

Panel a: Mean (± 1 SD) RMS deviations of steady-state pupil responses in infants, adults and the model eye in Experiment III. Panels b & c: Amplitude spectra of steady-state pupil responses of infants (panel b) and adults (panel c) in Experiment III. Gray traces show amplitude spectra from individual subjects and bold traces show the mean amplitude spectra. Panel d: Mean amplitude spectra of infants, adults and the model eye are compared. The steady-state fluctuations in pupil diameter were similar in infants and adults, with the fluctuations being slightly larger in infants than adults at low temporal frequencies. The steady-state fluctuations of both age groups were larger than those of the model eye.

Table 1

Details of the 2-factor ANOVA (Viewing condition \times Age) performed on the Δ pd, Δ acc and Δ verg data obtained in Experiment I. The Viewing condition and Age columns describe the main effect of these factors on Δ pd, Δ acc and Δ verg while the Viewing condition \times Age column denotes interaction between the two factors. The result of post-hoc Games–Howell testing (with no assumption of equal variance) for Age for Δ pd is noted in the text. Post-hoc testing for Age for Δ acc and Δ verg was not done because the main effect of age was not significant.

	Viewing condition	Age	Viewing condition \times Age
Δ pd	$F(1, 117) = 11.9$ $p = 0.001$	$F(2, 117) = 15.4$ $p < 0.001$	$F(2, 117) = 0.7$ $p = 0.51$
Δ acc	$F(1, 117) = 36.1$ $p < 0.001$	$F(2, 117) = 0.4$ $p = 0.23$	$F(2, 117) = 5.5$ $p = 0.005$
Δ verg	$F(1, 117) = 22.9$ $p < 0.001$	$F(2, 117) = 2.5$ $p = 0.09$	$F(2, 117) = 8.3$ $p < 0.001$

Table 2

Mean ratio of monocular response amplitude to binocular response amplitude for Δ_{pd} , Δ_{acc} and Δ_{verg} in the three different age groups in Experiment I. Error estimates are ± 1 *SD*.

	Age	Mono/Bino ratio
Δ_{pd}	Infants	0.46 ± 0.53
	Children	0.43 ± 0.46
	Adults	0.91 ± 1.29
Δ_{acc}	Infants	0.33 ± 0.19
	Children	0.32 ± 0.23
	Adults	0.82 ± 0.22
Δ_{verg}	Infants	0.38 ± 0.27
	Children	0.27 ± 0.24
	Adults	0.59 ± 0.21

Table 3

Details of the 3-factor ANOVA (Age \times Viewing condition \times Stimulus Amplitude) performed on the response amplitude at 0.1 Hz in Experiment II. The Age, Viewing condition and Stimulus amplitude rows describe the main effect of these factors on the response amplitudes while the Age \times Viewing condition, Age \times Stimulus amplitude, Viewing condition \times Stimulus amplitude and Age \times Viewing condition \times Stimulus amplitude rows denote the interactions between the three factors. Results of the post-hoc Games–Howell testing are noted in the text.

	Statistic
Age	$F(1, 225) = 13.77; p < 0.001$
Viewing condition	$F(1, 225) = 8.34; p = 0.004$
Stimulus amplitude	$F(2, 225) = 40.1; p < 0.001$
Age \times View cond	$F(1, 225) = 3.19; p = 0.08$
Age \times Stim amp	$F(2, 225) = 15.48; p < 0.001$
View cond \times Stim amp	$F(2, 225) = 2.49; p = 0.09$
Age \times View cond \times Stim amp	$F(2, 225) = 0.05; p = 0.96$