Characteristics of the Pupillary Light Reflex in the Alert Rhesus Monkey

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Clarke, Robert J., Hongyu Zhang, and Paul D. R. Gamlin. Characteristics of the pupillary light reflex in the alert rhesus monkey. J Neurophysiol 89: 3179–3189, 2003. First published January 15, 2003; 10.1152/jn.01131.2002. This study investigated the static and dynamic characteristics of the pupillary light reflex (PLR) in the alert rhesus monkey. Temporal characteristics of the PLR were investigated with Maxwellian viewing during sinusoidal changes in illumination of a 36° stimulus in both monkeys and humans. Bode plots of the PLR response were fitted by a linear model composed of a delay combined with a cascaded first- and second-order filter. The Bode magnitude plots conformed to this model with a sharp roll-off above 1.3 Hz for the human PLR and 1.9 Hz for the monkey PLR. Bode phase angle plots were fitted by this model with a delay of 280 ms for humans and 160 ms for monkeys. To investigate the influence of the sympathetic innervation of the iris on steady-state pupil diameter, dynamics of pupillary responses, and the latency of the PLR, we blocked this innervation pharmacologically with a selective alpha-1 adrenoreceptor antagonist. Although there was a resultant miosis (decrease in pupil diameter) from the relaxation of the pupil dilator muscle, no other measures of the PLR, including the dynamics and latency, were significantly affected by this treatment. We examined the pupillary responses evoked by visual stimuli presented either binocularly or monocularly at various locations on a 80° × 60° tangent screen. These pupillomotor fields revealed that, as has been reported for humans, stimuli at the fovea and surrounding macular region of monkeys produce substantially larger pupillary responses than more peripheral stimuli and that binocular responses are substantially greater than can be accounted for by the linear summation of binocular retinal illuminance. In conclusion, we found that the spatial characteristics of the PLR of the rhesus monkey are very similar, in all important aspects, to those reported for humans and that the temporal responses of the PLR are comparable between the two species. The rhesus monkey thus provides an excellent model for experimental studies of the neural control of the pupil.

INTRODUCTION

The pupillary light reflex (PLR) is the constriction of the pupil that is elicited by an increase in illumination of the retina. The direct PLR, which is present in virtually all vertebrates, is the constriction of the pupil in the same eye as that stimulated with light. The consensual PLR is the constriction of the pupil in the eye opposite to the one stimulated with light. It is generally accepted that the direct and consensual PLR are essentially equal in humans and monkeys (e.g., Loewenfeld 1958, 1993; Thompson 1992). The PLR has been extensively studied in humans (see Loewenfeld 1993 for a review). Many studies have concentrated on the dynamic response of the pupil to sine or square-wave changes in light intensity (e.g., Stark and Sherman 1957; Troelstra 1968). These studies provided information on the band-pass characteristics of the PLR and suggested that because of the apparently simple input/output characteristics of this reflex, it could be treated as a straightforward problem in servo analysis. However, it has also been known for many years that the magnitude of the PLR is dependent not only on the intensity of retinal illumination but also on the location of the stimulus (e.g., Johnson et al. 1988; Kardon 1995; Thompson et al. 1982). Pupillary responses elicited by peripheral stimulation have a low threshold and are small in amplitude, whereas pupillary responses elicited by foveal stimulation have a somewhat higher threshold but are much larger in amplitude (e.g., Kardon et al. 1995; Lowenstein et al. 1964). These characteristics of the PLR have received particular attention as they provide the framework for the rapidly expanding technique of objective visual field testing based on pupillometry (e.g., Johnson et al. 1988; Kardon 1992, 1995; Kardon et al. 1991; Thompson et al. 1982).

Because we are studying the neural control of the PLR in the alert behaving Rhesus monkey, we have investigated both the spatial and dynamic behavior of the PLR in this species and can compare our data to available human data. Preliminary reports of some of these findings have appeared previously (Clarke et al. 1994; Gamlin and Clarke 1996).

METHODS

Animal preparation

Four rhesus monkeys (Macaca mulatta; 3 male, 1 female, aged 3–8 yr) were used in this study. All experimental procedures were approved by the Institutional Animal Care and Use Committee and complied with the National Institutes of Health Policy on Humane Care and Use of Laboratory Animals. Surgical procedures that have been reported previously are only briefly described (Gamlin et al. 1989, 1994). Animals underwent three aseptic surgical procedures under pentobarbital sodium anesthesia. Postsurgically they received analgesics to minimize pain. Animals were first implanted with a stainless steel head-holder and, 6–12 wk later, with bilateral search coils (Fuchs and Robinson 1966; Judge et al. 1980).

Stimulus presentation

Experiments were run in an apparatus that allowed for a variety of stimulus conditions (Fig. 1). By the appropriate movement or illumination of specific display elements, this apparatus could be used as a back-projection tangent screen or as a Maxwellian viewing system, as described in the following text.
TANGENT SCREEN. To use the back-projection screen, located 45 cm in front of the animal, the optical benches and optometer, which are on stepper-controlled platforms, were retracted. A fixation spot of 0.5° from a red laser diode was projected onto the tangent screen with XY galvanometers (General Scanning 325DT), while another XY galvanometer system could project white circular stimuli anywhere within an 80° horizontal by 60° vertical range. The size of the stimulus was varied by a stepper-controlled iris, and its luminance was controlled using a stepper-controlled neutral density filter wheel placed in the light pathway. Stimulus presentation was controlled with an electro-magnetic shutter (Uniblitz). All stimulus parameters were computer controlled. Visual stimuli could be presented to both eyes, or to either eye, independently by covering one eye with an occluder composed of an infrared pass glass filter cut to shape. The infra-red pass properties of the occluder were such that a CCD camera could view the pupil of the occluded eye while preventing visible light from entering the eye. For many of the experiments, a background luminance of 10⁻⁴ cd/m² was maintained on the screen.

MAXWELLIAN VIEW DISPLAY. Under normal viewing conditions, such as viewing a tangent screen, the PLR is under a closed loop condition and changes in pupil diameter will modulate the light entering the eye. It is however often useful to study changes in pupil diameter under open loop conditions, and this can be achieved by presenting a visual stimulus under Maxwellian view. To do so, the optical benches and optometer were in their advanced position as depicted in Fig. 1. This arrangement permitted the animal to view through the optical system instead of viewing the tangent screen. The optics of this system are relatively straightforward and are based on the original design of Crane and Clark (1978). The lenses L₁-L₄ are doublets of two achromatic lenses each of 200-mm focal length yielding an effective focal length of 106 mm. The lenses are 75 mm in diameter, allowing nearly ± 18° field of view. These lenses serve as optical relays and form an image of each eye at the focal point of lenses L₅ and L₆, which are F₁.4, 50-mm focal-length camera lenses. Lenses L₇ and L₈ are F₃.5, 150-mm focal-length enlarger lenses. To produce Maxwellian viewing in this apparatus, 5-mm-diam green light-emitting diodes (LEDs) are placed in the optical systems serving each eye (see Fig. 1) and are imaged at the pupil plane of each eye (LE and RE, respectively). Due to the ratio of the focal lengths of lenses L₅ and L₆ to those of lenses L₇ and L₈, the LED images in the pupil plane were 1.67 mm in diameter and fell well inside the pupils under all conditions. The LEDs could be viewed monocularly or binocularly. Illumination intensity was controlled by changing the duty cycle of a 1-kHz, square-wave signal driving the LEDs. The duty cycle, which was under computer control, could be reliably varied by a factor of a thousand, and this provided a range of retinal illumination of 3 log units that could be modulated in a square or sinusoidal fashion over a wide range of frequencies. An optometer based on the design of Kruger (1979) was positioned so that accommodation could be measured in the left eye.

Behavioral training and eye-movement recording

For visual probe trials with the tangent screen or for Maxwellian viewing, animals were trained to fixate the red laser spot for a juice reward while the stimulus was presented. A brief tone at the beginning of each trial alerted the monkey to the impending task and served to minimize any variation in pupil diameter due to changes in alertness. The horizontal and vertical gains of each eye were calibrated independently at the beginning of each recording session. This was done by requiring the animal to fixate, with either eye alone, targets that appeared at various horizontal and vertical positions. Animals showed little variability in fixation during trials, and saccades of <0.2° could be reliably detected. Pupil diameters were measured in both eyes under infra-red illumination using video cameras and ISCAN RK406 pupillometer systems. Due to the 60-Hz sampling rate of video-based pupillometers, there is a delay in their response. By producing rapid changes in the diameter of an artificial pupil, we measured this delay as 24 ms, which was subsequently factored into all latency measurements. Pupil diameters, accommodation, and the positions of both the right and left eyes were stored at 333 or 500 Hz to computer disk along with target parameters for analysis after the experiment.

Data analysis

The stored data were analyzed off-line using a computer equipped with interactive graphics. For analysis of sine wave data collected

![FIG. 1. Schematic diagram of the system used for presentation of visual stimuli. The monkey’s head is fixed in a stationary position within the apparatus. The left eye (LE) could observe targets generated on monochrome television monitors through lenses L₁, L₃, and L₅ via mirrors M₁ and M₃, respectively, and the right eye (RE) could observe targets through the lenses L₂, L₄, and L₆ via mirrors M₂ and M₄, respectively. The lenses L₇ and L₈, respectively, could be moved in or out (as indicated by arrows) to change the apparent distance of the image providing a stimulus to accommodation without changes in luminance or size. LEDs were placed in the optical pathway and focused at the pupil plane to provide a Maxwellian stimulus to each eye. An optometer was positioned in front of 1 eye to measure the state of accommodation in that eye. The optometer and lenses were mounted on motorized sliders so these systems could be moved out (arrows indicate the directions of possible movement) to allow a clear view of the tangent screen.](http://jn.physiology.org/)
with Maxwellian viewing, we used Matlab to perform analyses needed to derive the gain and phase of the pupillary response with respect to the input signal. The gain of the response was defined as the change in pupil area as a function of the change in retinal illumination. Thus a gain of 1.0 would indicate that the pupil area had decreased precisely to match the increase in illumination.

For our other analyses, we measured pupillary responses with respect to transient constriction, steady-state constriction, and latency of constriction. Details of these measurements are shown in Fig. 2, which depicts a typical pupil response to a 5°, 30 cd/m² stimulus projected on the tangent screen at the fixation point. Prior to stimulus onset, during the period that the animal is fixing the dim laser target, the pupil is relatively dilated. After stimulus onset there is a delay prior to pupilloconstriction. After this delay, at low or intermediate luminance, the pupil constricts and reaches its minimum size (transient response) in 500–1,000 ms and then often redilates (commonly referred to as pupillary escape) to a slightly less constricted diameter for the duration of the stimulus light on (pupillary capture). Four measurements were taken from each response: the mean pupil diameter during the fixation period prior to stimulus light onset, the mean pupil diameter during the constant constriction phase, measured not less than 2 s after stimulus onset and after the transient phase, the delay between stimulus onset and initial pupilloconstriction, i.e., latency, and the maximal pupilloconstriction during the transient phase. This latter component of the response will be referred to as the transient pupil response in this paper.

The relationship between the intensity of illumination and mean steady-state pupil diameter was fit with the following function: pupil diameter  =  \( D_{\text{max}} = \left( C_{\text{max}} \times (I_\text{B} / (I_\text{B} + C)) \right) \); where \( D_{\text{max}} \) is the maximal pupillary diameter, \( C_{\text{max}} \) is maximal pupilloconstriction, \( I_\text{B} \) is a constant, and \( C \) is proportional to the intensity at which half-maximal pupilloconstriction is produced. The relationship between the intensity of illumination and transient pupilloconstriction was fit with the following function: pupilloconstriction  =  \( C_{\text{max}} \times (I_\text{B} / (I_\text{B} + C)) \); where \( C_{\text{max}} \) is maximal pupilloconstriction, \( B \) is a constant, and \( C \) is proportional to the intensity at which half-maximal pupilloconstriction is produced. The relationship between PLR latency and stimulus intensity over the tested range was well fitted by a function of the form: latency  =  minimum latency  +  \( k \times I^{-\gamma} \), where \( I \) is illumination in trolands, and \( k \) and \( \gamma \) are constants.

To compare the pupillary responses elicited by binocular stimulation with those elicited by monocular stimulation, we adopted a quantitative treatment similar to that used by Varjú (1967b) and Doesschate and Alpern (1967). This approach assumes that the pupillary responses elicited by binocular stimuli can be described by combining the monocular pupillary responses while taking into account their influence on one another through forward shunting inhibition. More specifically, if the outputs of the two retinas are \( x \) and \( y \), the amount of pupil constriction is \( z \), and \( k_1 \) and \( k_2 \) are constants related to the degree of forward shunting inhibition, then the following equation is obtained

\[
z = \frac{x}{1 + k_1y} + \frac{y}{1 + k_2x}
\]

During monocular stimulation, \( z \) will reduce to either \( x \) or \( y \), and these variables can then be used to estimate the values of \( k_1 \) and \( k_2 \) during binocular viewing.

**Pharmacological sympathectomy**

The sphincter iris muscle receives its innervation via parasympathetic cholinergic postganglionic fibers, while the radial dilator muscle receives inputs from sympathetic noradrenergic fibers which act on alpha-1 adrenergic receptors on the dilator muscle. The difference in these smooth muscle receptors was exploited here to determine the contribution of sympathetic input to the dynamic and static components of the PLR. The sympathetic input to the iris was blocked pharmacologically with topical applications of eye drops containing dapiprazole HCl (0.5%) (Rev-eyes), a selective alpha-1 adrenoceptor antagonist (e.g., Eltz 1997; Valeri et al. 1988). After administration of the dapiprazole HCl, a miosis resulting from the relaxation of the pupil dilator radial smooth muscle was observed to last for approximately 6 h.

**Human subjects**

To allow comparisons with our data from the Rhesus monkey and with earlier published reports in humans (e.g., Stark and Sherman 1957; Troelstra 1968), two subjects (1 male, 38 yr; 1 female, 24 yr) were used to obtain the normal temporal data needed to generate the magnitude and phase Bode plots required to investigate the frequency response of the human PLR. The gain and phase data obtained from these two subjects was not significantly different. One of these two subjects was then used to investigate the effects on the PLR of pharmacological sympathectomy of the iris using Dapiprazole HCl. Informed consent was obtained from both subjects and all IRB regulations were observed.

**Results**

**Pupillary responses with Maxwellian viewing**

**Step changes in illumination**. We studied the steady-state and transient characteristics of the pupil during binocular and monocular Maxwellian presentation of a large-field stimulus at various levels of retinal illumination. Because there was no significant anisocoria with either binocular or monocular viewing, data for the pupil diameter of only one eye are presented. Similar results were obtained in all monkeys studied, and the data shown below are thus representative. Under normal conditions, the response of the pupil to an increase in illumination of 10 Td is shown in Fig. 3, top. This may be compared with the pupil response shown in Fig. 3, bottom, which was recorded after iris sympathectomy. The relaxation of the dilator muscle results in a clear miosis, such that resting pupil diameter decreases from approximately 6.5 to 5 mm. However, as shown in the following text, the amplitude and dynamics of the pupillary responses are virtually unaffected. This reflects a

![Image](http://jn.physiology.org/)

**FIG. 2. Analysis of pupillary responses. Bottom**: the timing of stimulus presentation. **Middle**: a continuous record of pupil diameter over 8 s during which the monkey was required to fixate a dim red target on a tangent screen while, 1.5 s after the beginning of the trial, a 5°, 30 cd/m² light stimulus was presented at the fixation point. The pupil response to this stimulus shows all the features analyzed in this study. Period 1 represents the time over which mean pupil diameter was measured prior to stimulus onset. Period 2 represents the time over which mean pupil diameter was measured during the constant constriction phase. Period 3 represents the latency measurement. Time point 4 indicates how maximal pupilloconstriction during the transient phase was determined. **Top**: the velocity of pupil diameter changes. The velocity trace is inverted for convenience. Scale bar represent 1 mm and 5 mm/s.
dominant contribution of the parasympathetic input to the transient responses of the PLR.

These steady-state and transient responses were examined systematically. Figure 4, A and C, shows steady-state pupil diameter during binocular (A) and monocular (C) viewing as a function of retinal illumination for the normal and sympathectomized iris. The data in this and the other panels in this figure were fitted as described in METHODS. The binocular pupillary responses in this case are closely fitted by the forward shunting inhibition model using values of \( k_1 = k_2 = 0.15 \). Note that the pupil in the sympathectomized condition is approximately 2 mm more constricted than normal but that the light-evoked reduction in pupil diameter is comparable to the normal condition throughout the tested range.

Figure 4, B and D, shows transient pupilloconstriction during binocular and monocular viewing, respectively, as a function of retinal illumination for the normal and sympathectomized iris. Interestingly, the binocular pupillary responses in this case are closely fitted by the forward shunting inhibition model using values of \( k_1 = k_2 = 0.3 \). Also note that, during binocular visual stimulation (Fig. 4B) with moderate increases in illumination (less than approximately 30 Td), the transient pupilloconstriction has approximately the same amplitude under both sympathectomized and normal conditions. However, it is reduced in magnitude for greater increases in illumination in the sympathectomized condition, presumably due to iris mechanics (see DISCUSSION). In contrast, under monocular visual stimulation (Fig. 4D), the transient responses were equal in amplitude under the two conditions.

Influence of stimulus luminance on response latency

Using the same Maxwellian viewing conditions as described in the preceding text, we investigated the latency of the PLR to stimuli of varying intensities (Fig. 5). This figure presents latency data for the normal and sympathectomized conditions under binocular (Fig. 5A) and monocular conditions (Fig. 5B). The relationship between latency and stimulus intensity (in trolands), which were well fit by a power function (METHODS), demonstrated that under our viewing conditions, the minimum latency of the PLR was 150 ms binocularly and 160 ms monocularly. The latency increased from this minimal value by approximately 200 \( \pm \) 1.2 ms in all cases.

To further characterize the temporal characteristics of the PLR, it was investigated with binocular Maxwellian viewing of sinusoidal changes in illumination. Figure 6, which shows pupillary responses to sinusoidally modulated light ranging in frequency from 0.1 to 10 Hz, clearly indicates that the sinusoidal modulation of pupil diameter declines rapidly above 2 Hz for the monkey. Figure 6 also shows that, despite a decrease in modulation of pupil diameter with increasing temporal frequencies, pupil size nevertheless continues to decrease until temporal frequencies well above 5 Hz are reached. For example, although pupil diameter is modulated significantly less at 4 Hz (Fig. 6E) than 0.2 Hz (Fig. 6A), the pupil is nevertheless more constricted at 4 Hz (Fig. 6G).
The results from these temporal experiments were analyzed with traditional Fourier techniques. Figure 7, A and B, shows that the frequency response characteristics of the PLR are similar for the rhesus monkey (H11001) and human (H9004), as displayed in Bode gain and phase plots. To determine the contribution of the sympathetic innervation of the iris to the overall dynamics of the PLR, we investigated the frequency response characteristics of this reflex after chemical sympathectomy of the iris (Fig. 7, C and D). Apart from a small reduction in the magnitude of the PLR in humans and a slight improvement in frequency response for both monkeys and humans, chemical sympathectomy produced no major effects on PLR dynamics.

The data from normal subjects were fitted with a model composed of a cascaded delay and first- and second-order filters. For the rhesus monkey, the data were best fit by a delay of 160 ms, a first-order filter with a time constant of 0.12 s, and a second-order filter with a resonant frequency of 1.9 Hz and a damping constant of 0.5. For the human, the data were best fit by a delay of 280 ms, a first-order filter with a time constant of 0.15 s, and a second-order filter with a resonant frequency of 1.3 Hz and a damping constant of 0.7. Although this model adequately fitted both the gain and phase data for the rhesus monkey, it failed to fully fit the phase advance seen in the human data at low temporal frequencies.

Influence of stimulus location on pupillary responses

To investigate pupillary responses to stimuli of varying size and intensities presented at different locations within the visual field, the tangent screen display was used.

Spatial characteristics. Steady-state pupillary responses. Figure 8 shows steady-state pupillary responses to a 5° stimulus presented at three different luminances in different parts of the visual field during binocular (A–C) and monocular (D–F) viewing. At the lowest luminance used, the pupil responds almost exclusively to central field stimulation. At higher luminance...
nances, the pupil responds to stimuli placed at all positions in the visual field, but the central field responses increase in amplitude proportionately. It is also clear from these figures that binocularly elicited pupil responses (Fig. 8, A–C) are significantly larger in amplitude than monocular responses (D–F). Indeed, the pupil responses elicited by 3 cd/m² stimuli during binocular viewing (Fig. 8B) are almost as large as the pupil responses elicited by 30 cd/m² stimuli during monocular viewing (Fig. 8D).

**Transient pupillary responses.** Figure 9 shows transient pupillary responses to a 5° stimulus presented at three different luminances in different parts of the visual field during binocular (A–C) and monocular (D–F) viewing. At the lowest luminance used the pupil responds transiently to stimuli placed at all positions in the visual field, but the central field responses are larger. At higher luminances, the pupil responses to stimuli placed in the more peripheral visual field increase substantially, but the central field responses do not increase in amplitude proportionately. During monocular viewing, pupil responses are of lower amplitude than binocular responses and do not display as pronounced a foveal response as is seen during binocular viewing.

**Luminance sensitivity and spatial summation characteristics.** To more extensively investigate the interactions between stimulus characteristics and location, the area and intensity of stimuli at five locations were systematically varied (Fig. 10). The stimuli were presented either at the fovea, or in one of the four quadrants. Figure 10 shows the results during binocular (A and B) and monocular (C and D) viewing. The pupil responses elicited from the central retina are larger and have a lower threshold than those pupilary responses elicited by stimuli in the four retinal quadrants whether luminance (A and C) or stimulus area (B and D) are varied. Pupillary constriction shows broad spatial summation irrespective of whether it is elicited by an equivalent increase in stimulus intensity or stimulus area. Overall, these pupilary responses were closely related to the total energy of the retinal illumination, and they showed broad spatial summation for stimuli as large as 20° in diameter. Again pupilloconstriction was substantially greater with binocular viewing. We quantified this difference using the forward shunting inhibitory model described earlier and found for central visual stimulation that the binocular pupilary responses were closely fitted by a model using values of $k_1 = k_2 = 0.15$. In contrast, we found for peripheral visual stimulation, that binocular pupilary responses were more closely fitted by a model using values of $k_1 = k_2 = 0.2$.

**DISCUSSION**

There have been few previous studies of the characteristics of the PLR in macaque monkeys. An early study by Carpenter and Pierson (1973) examined the effects of pretectal lesions on the pupillary responses elicited by a stimulus of 2 ft.-cd presented through a fiber optic system placed 1 in from the eye. In 1978, Barlow and colleagues examined the PLR of the awake monkey in response to 3-s Ganzfeld flashes that ranged from $10^{-8}$ to 1 L in intensity. A recent study from our laboratory examined the effects of stimulus color, structure, and light flux increments on the PLR in the rhesus monkey (Gamlin et al. 1998). That study did not examine aspects of the PLR that are comparable with those examined in the present paper. In a separate study, Heywood and colleagues (1998) examined the pupillary responses to achromatic and chromatic grating stimuli in rhesus monkeys. In a study by Pong and Fuchs (2000); the metrics of the PLR were examined under monocular and binocular stimulus conditions in which LEDs were placed 50°.

**FIG. 7.** Gain (A) and phase (B) relationships of the pupillary responses to sinusoidal light stimulation for the normal monkey (+) and human (Δ) iris. Gain (C) and phase (D) relationships of the pupillary responses to sinusoidal light stimulation for the pharmacologically sympathectomized monkey (+) and human (Δ) iris. In A, the data for the gain of the primate pupillary light reflex (PLR; +, ···) were fit by a 3rd-order function with the parameters specified in RESULTS. The data for the gain of the normal human PLR (Δ) were also fit by a 3rd-order function. For reference, these 2 curves are redrawn in C for the pharmacologically sympathectomized condition. In B, the data for the phase of the primate PLR (+, ···) were fit by a 3rd-order function and delay with the parameters specified in RESULTS. The data for the phase of the normal human PLR (Δ) were also fit by a 3rd-order function and delay. For reference, these 2 curves are redrawn in D for the pharmacologically sympathectomized condition.
temporal of straight-ahead and stimuli ranging in intensity from 5 to 28,800 cd/m² were presented for either 0.1 or 1 s. The stimulus configuration used by Pong and Fuchs in their study did not allow for open-loop PLR measurements to be made nor did it allow for photic stimulation of a localized retinal region. In the present study, Maxwellian viewing enabled us to examine pupillary responses to stimuli of various intensities and temporal frequencies under open-loop conditions. We also used a tangent screen system to examine the PLR in response to stimuli that were systematically varied in area, intensity, and visual field location.

**PLR frequency response**

We compared the gain and phase of the PLR between rhesus monkeys and humans under both normal and chemically sympathectomized conditions. As has been previously reported for humans (e.g., Stark and Sherman 1957), we found that a third-order model could match the gain and phase responses for both humans and rhesus monkeys. We also found that sympathectomy had little effect on the gain or phase of the PLR in either monkeys or humans. Our results in humans are very similar to those of Stark and Sherman (1957). The only difference between our results is that we observed a more rapid roll-off in the gain of the pupillary response. For example, we found that at 3 Hz, modulation of pupillary diameter was reduced more than 10-fold, whereas Stark and Sherman observed only about a sixfold reduction. This relatively minor difference is most likely explained by differences between the stimulus configuration and characteristics used in the two studies.

More importantly, our results show that some significant differences exist between humans and rhesus monkeys in dynamic measures of the PLR. First, the theoretical resonant frequency of the PLR under the stimulus conditions used was approximately 50% higher in rhesus monkeys than in humans (1.9 Hz for the rhesus monkey vs. 1.3 Hz for humans), and the delay required to best fit the phase characteristics of the PLR was 120 ms shorter in rhesus monkeys than in humans (160 ms for the rhesus monkey vs. 280 ms for humans). These findings lead to the conclusion that the PLR of the rhesus monkey has both a significantly shorter latency and a faster response than that of humans. The latency difference of the PLR and possible explanations for this significant difference are discussed more fully in the next section.
We also found, as has previously been reported for humans for sinusoidal stimulus intensity modulation (e.g., Varjú 1964), that the average pupillary diameter was reduced between 0.2 and 5 Hz, reaching a minimum at 1–2 Hz, and redilated above 5 Hz. As has been suggested by Varjú (1964), this effect could result if an apparent brightness enhancement effect existed for the PLR that is comparable to the Brücke-Bartley brightness enhancement effect of flickering lights (Bartley 1938). Such brightness enhancement has been modeled by a broad temporal filter followed by a single accelerating nonlinearity (Wu et al. 1996).

Influence of illumination intensity on pupilloconstriction latency

We found that the latency of pupilloconstriction increased nonlinearly with decreases in stimulus intensity. More specifically, we found that as stimulus intensity decreased, the latency increased from the minimum latency by an amount proportional to the inverse of the square root of the intensity. In contrast, the only other study (Pong and Fuchs 2000) that has previously investigated this issue in the rhesus monkey found that the relationship between response latency and stimulus intensity could be fit linearly. While some studies in humans (e.g., Cibis et al. 1977; Lee et al. 1969) have also been able to fit their results with a linear fit, others (e.g., Lowenstein et al. 1964) have shown a relationship between latency and stimulus intensity that is very similar to the one reported here. There are a couple of obvious explanations for the differing results. First, the size, location, and means of stimulus presentation varied between each of the studies. Alternatively, the way in which the onset of pupilloconstriction was determined may have varied between studies, which would also account for the differing results.

The pupilloconstriction latency differences reported here between humans and primates for both static and dynamic visual stimuli are similar to those that we have reported previously (Gamlin et al. 1998) and comparable with those reported by Pong and Fuchs (2000). The explanation for this substantial latency difference between these two species is not immediately obvious. It seems unlikely to be explained by a difference in speed of sensory processing and can only be partially explained by the shorter neural conduction distances in the rhesus monkey. Perhaps these two species differ with respect to the contraction latency and speed of the sphincter.
pupillae muscle. Whether these proposed muscular differences result from anatomical or physiological (biochemical) differences remain to be determined.

**Direct and consensual pupillary responses**

In the animals examined for this study, we found that the direct and consensual pupillary responses were essentially the same in amplitude under all the stimulus conditions that we used. This is consistent both with other experimental findings in rhesus monkeys (Carpenter and Pierson 1973; Loewenfeld 1958) and with the generally accepted idea that the direct and consensual PLR are essentially equal in humans and monkeys (e.g., Loewenfeld 1993; Thompson 1992). In humans, very slight asymmetries have previously been reported (Wyatt and Musselman 1981), but in the rhesus monkey, a recent study reported large differences between the direct and consensual responses (Pong and Fuchs 2000). In both the present study and that by Carpenter and Pierson (1973), the diameters of both pupils were measured concurrently and no significant anisocoria was observed. It is likely that the apparent finding by Pong and Fuchs that the consensual response is less than the direct response in rhesus monkeys is a result of their use of nonconcurrent pupillary measurements. However, it is possible that presentation of the stimulus at 50° temporal of straight-ahead might result in a larger direct than consensual response. This possibility would need to be determined experimentally with concurrent measurement of the diameters of both pupils.

**Binocular summation**

Our results demonstrated that, with either Maxwellian viewing or tangent screen stimulus presentation, binocularly presented stimuli elicited significantly larger pupillary responses than monocularly presented stimuli but are not simply additive. Comparable binocular summation has been observed previously in humans for the pupillary responses to monocular and binocular stimuli (Doesschate and Alpern 1967; Varju, 1967a,b), and a mathematical treatment based on forward shunting inhibition was developed by these authors to quantify the binocular interactions seen under these conditions (see METHODS). Using this approach in humans, it was reported that for steady-state stimuli of 2,000 Td, the values of $k_1$ and $k_2$ were approximately 0.2 (Doesschate and Alpern 1967). In the rhesus monkey, we found comparable values (between 0.15 and 0.2) with those in humans for steady stimuli but found that the values for $k_1$ and $k_2$ increased to 0.3 for measures of the transient pupillary response. This suggests that binocular summation may be reduced during the initial transient visual input to the PLR. This would be consistent with psychophysical observations of binocular summation that show significant summation for low to intermediate temporal frequencies but not for high temporal frequencies (Cavonius 1979). One can speculate that this proposed model of forward shunting inhibition in the PLR may have a neural correlate in the synaptic triadic arrangement that has been reported in the pretectal olivary nucleus (Campbell and Lieberman 1985; Klooster and Vrensen 1997). In this triadic arrangement, a retinal terminal contacts both the den-
drite of a PON neuron and a GABAergic terminal. The GABAergic terminal, in turn, contacts the dendrite thus forming a forward connection that can produce shunting inhibition of the direct retinal input.

**Contribution of sympathetic innervation to pupillary responses**

The sympathetic pathway innervates the radial iris muscle that dilates the pupil. The pupillodilator sympathetic pathway runs from the ciliospinal centers of Budge and Waller to the superior cervical ganglion in the neck that in turn innervates the radial iris muscles via noradrenergic postganglionic fibers (Loewenfeld 1993; Thompson 1992). Normally the sympathetic pathways provides a tonic drive to the dilator iris muscles. The loss of this tonic drive can occur in certain types of injuries and results in a characteristic pupill constriction or Horner’s pupil (Loewenfeld 1993; Thompson 1992). We examined the contribution of this sympathetic pathway both to the regulation of tonic pupil size and to the dynamics of pupilloconstriction by pharmacologically removing the sympathetic input. We observed a tonic pupil constriction consistent with that reported in Horner’s syndrome but very little direct effect on pupillary dynamics. The range of pupilloconstriction was restricted by the mechanical limitation imposed by the tonic constriction that resulted from the chemical sympathectomy. Thus for brighter visual stimuli, pupillary dynamics were affected due to pupil size as reported in humans (Loewenfeld and Newsome 1971). However, for smaller pupillary changes resulting from either step or sinusoidal changes in illumination, the dynamics were very similar under both the normal and sympathectomized condition. In conclusion, this study clearly indicates that the parasympathetic pupillconstrictor input is most important dynamically but that the sympathetic pupillodilator input nevertheless acts slowly to modulate pupil diameter under steady-state conditions.

**Pupillomotor fields**

In humans, it has previously been shown that the pupillary responses elicited by peripheral stimulation have a low threshold and are small in amplitude, whereas pupillary responses elicited by foveal stimulation have a somewhat higher threshold but are much larger in amplitude (e.g., Kardon et al. 1995; Lowenstein et al. 1964). In addition, in many subjects the pupillary responses elicited by stimuli in the temporal field (nasal retina) are larger than the responses to the same stimuli in the nasal field (temporal retina) (e.g., Kardon et al. 1991). These characteristics of the PLR have received particular attention as they provide a means for additional visual field testing based on pupillometry (e.g., Johnson et al. 1988; Kardon 1992, 1995; Kardon et al. 1991; Thompson et al. 1982). Our findings in the rhesus monkey are entirely consistent with those in humans. We found that the pupillomotor responses elicited by centrally presented stimuli are substantially greater for than those elicited by stimuli presented in the more peripheral retina. We also found that in two of the four tested animals, the pupillary responses elicited by stimuli in the temporal field were larger than the responses to the same stimuli in the nasal field.

**Conclusion**

The only significant difference between the PLR of rhesus monkeys and humans is that the latency of the reflex is significantly shorter (approximately 120 ms) in the rhesus monkey. In all other measures, the results of this study and those of a previous study by us (Gamlin et al. 1998) indicate that the PLR in rhesus monkeys is remarkably similar to that in humans.

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