Behavioral Perimetry in Monkeys

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Purpose. Normative data on the systematic changes in visual sensitivity as a function of retinal eccentricity have provided the basis for efficient threshold strategies and data analysis routines for static perimetry. The standard methods of assessing visual field changes in patients also could be used for monkeys with experimentally induced ocular disorders if the normal visual fields of monkeys and humans were similar.

Methods. Normal visual field data from three rhesus monkeys were compared to data from eight human subjects using the standard threshold programs of the Humphrey Field Analyzer.

Results. The experimental paradigm developed for these measurements provided excellent behavioral control for the monkeys, with reliability indices well within acceptable limits. The visual field data from monkeys were comparable to those from humans with respect to: (1) sensitivity as a function of stimulus field size; (2) the derived Statpac global indices; and (3) the variance of threshold measurements across the visual field.

Conclusion. The visual fields of monkeys and humans are similar, and the techniques of computerized perimetry may be applied to monkey subjects without significant modification. Invest Ophthalmol Vis Sci. 1993;34:31–40.

Computerized static perimetry is the preferred method for assessing functional peripheral vision defects associated with ocular disorders.[1,2] The primary advantages of computerized perimetry over manual perimetry are a result of more sophisticated psychophysical methodology and data analysis procedures. These advantages were made possible by the application of computer technology to perimetry. However, to make computerized perimetry a practical and efficient clinical procedure, algorithms were developed that based individual test decisions on an empiric model of the "hill of vision" of normal observers.[3] For example, the initial intensity levels for quantitative threshold perimetry are set at levels based on the expected threshold of a normal observer.[4] In addition, the significance of overall deviations or patterns of deviations across the visual field (ie, the perimetry global indices) is quantified with respect to the mean and variance of the visual field data of normal, age-matched observers.[5]

The threshold strategies and statistical analyses of perimetry data commonly used with clinical patients also could be employed to study monkey models of ocular disorders (eg, experimental glaucoma in monkeys[6]) if the characteristics of the normal visual fields of monkeys and humans were similar. Previous studies have shown excellent agreement between these two species for psychophysical functions of foveal vision.[7–9] However, systematic comparisons of peripheral vision sensitivity of macaque monkeys and humans have not been made. The inter-species comparisons of

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visual fields could be expedited if the data for monkeys were obtained with clinical instrumentation, because normative data on humans are available for these instruments. Moreover, subsequent data on experimental ocular pathology in monkeys could be more easily interpreted by established clinical criteria and generalized to the human condition more directly. Therefore, the objectives of the present study were to: (1) develop the methods required for behavioral perimetry with monkeys using standard clinical instrumentation; and (2) obtain visual field data for normal monkeys for comparison with data from human subjects.

MATERIALS AND METHODS

Subjects

Three 5-yr-old male rhesus monkeys (*Macaca mulatta*) and eight men 24–50 yr old were used as subjects. All experimental and animal care procedures adhered to the ARVO Statement for the Use of Animals in Ophthalmic and Vision Research. For the human subjects, tenets of the Declaration of Helsinki were followed, informed consent was obtained, and institutional human experimentation committee approval was granted. The human subjects were students or faculty members who were known to have normal vision and to be free of ophthalmic disorders. The refractive errors of six of the human observers were near emmetropia, whereas the other two had low myopia (<3.00 diopters) and did not use spectacle lenses during the perimetry tests. For the monkeys, ophthalmoscopy and retinoscopy under cycloplegia did not reveal any ocular abnormalities or significant refractive errors. Subjects of both species were well-practiced before the perimetry data were collected. Each of the human observers had at least two prior measurements and the monkeys had undergone several months of training for behavioral perimetry before data collection.

Apparatus

The visual field data for the human subjects were obtained using a conventional Humphrey Field Analyzer Model 630 (Allergan Humphrey, San Leandro, CA), whereas the visual fields of the monkeys were measured with a modified perimeter of the same type. For the field analyzer used with monkeys, the instrument shrouding and patient head support were removed and the perimeter was attached to a small primate testing cubicle (BRS/LVE, Laurel, MD). The interfacing wall of the cubicle was removed and replaced with a sheet-metal partition that incorporated a viewing port centered in the perimeter bowl, a juice-reward delivery spout, and the monkeys' behavioral response lever. A custom-made primate chair, inside the testing cubicle, provided adjustments for aligning the monkeys during field testing. An additional set of lights (tungsten lamps with Schott glass RG-715 filters; Jenaer Glaswerk Schott and Gen, Mainz, Germany) mounted on the cubicle wall provided infra-red illumination for the video eye position monitor (Fig. 1), but did not affect the calibrated intensity of the perimeter bowl.

Several modifications were made to the manufacturer's programmed sequence for visual field testing to attain better behavioral control during the perimetry measurements, but these modifications did not alter the standard threshold procedures or the data analysis programs of the perimeter. The most important modifications were the following. (1) a light emitting diode (LED), located behind the fixation aperture of the perimeter bowl, was imaged at the position of the subject's pupil during testing (Fig. 1). This Maxwellian-view system assisted in the behavioral control of the monkey's head position and fixation, because a luminance increment of the fixation LED was the stimulus in at least 30% of the session trials; therefore, it was the most probable location of a visual stimulus throughout the session. The LED subtended a 1° visual angle at the entrance pupil of the eye, and its intensity was controlled by variations of the pulse-to-duty cycle of the LED voltage at a 100 Hz constant flicker rate. (2) As an additional method to control the monkey's fixation, an infra-red-sensitive video camera for a microprocessor-based eye position monitor (Micromeasurements System 1200, Micromeasurements, Inc., Berkeley, CA) was coaxial with the LED fixation stimulus, as illustrated in Figure 1. The eye monitor was sensitive to eye movements of 4°–5°, and during each trial, eye movements larger than this "window" caused the trial to be aborted. (3) Custom read-only memory chips for the field analyzer were obtained from the manufacturer to eliminate movement of the perimeter projector as a cue to the stimulus presentation and to allow data acquisition using discrete trial-by-trial procedures. With the custom chips, the projector's movement to its next test field location was delayed by approximately 2 sec after each trial. The subject's response interval for detected stimuli was restricted to a 0.9 sec period after the perimeter's shutter opening. (4) The input from the subject's response button was channeled through an external computer that controlled the experimental processes. The perimeter response switch was held closed throughout each trial fore period, until the visual field stimulus was to be presented. In addition, the response was inverted so the monkeys released their response lever to indicate a detected stimulus, rather than press the response button (see the behavioral methods).

Methods

Luminance increment-thresholds for the central fixation stimulus and the peripheral visual field stimuli were measured using the criterion response interval

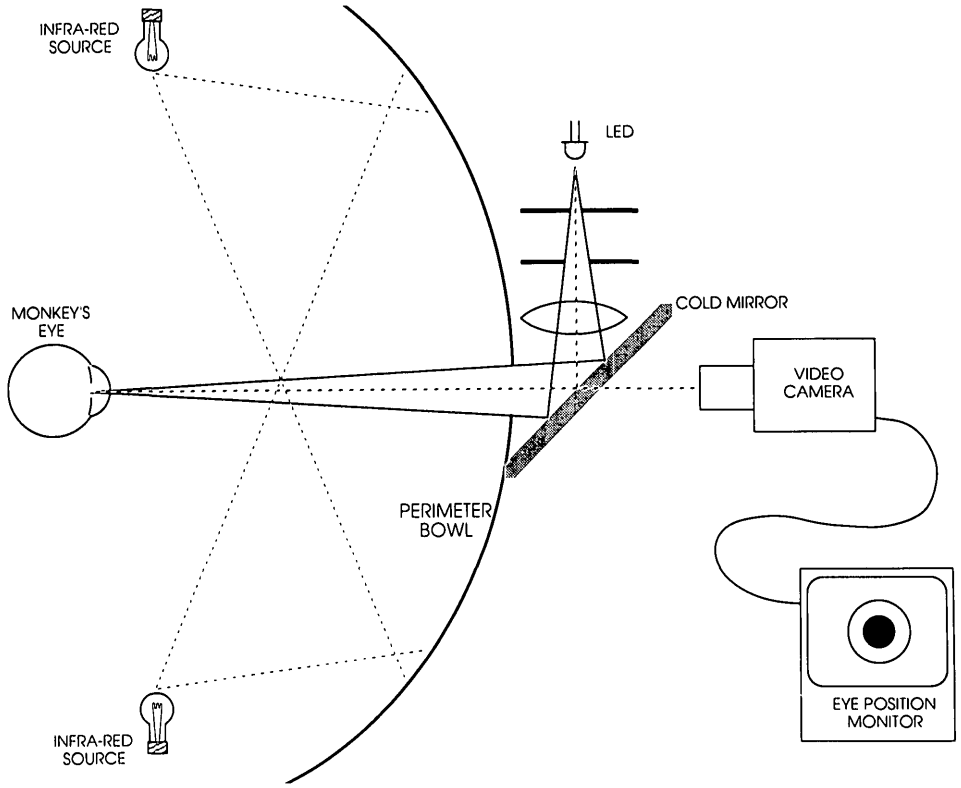

FIGURE 1. Schematic of the modified perimeter. (See text for details.)

procedure that we used in several previous psychophysical studies of visual functions of monkeys.[10,11] This procedure was easily adapted to the field analyzer, because the behavioral requirements for threshold measurements with clinical patients are similar to those of the monkey psychophysics paradigm. The main components of the behavioral methods are presented in the block diagram in Figure 2. The availability of a trial was indicated by the onset of an auditory signal—ie, a ready tone. In the presence of the ready tone, the monkey could initiate a trial-stimulus fore period by pressing the response lever. The fore period, randomized for durations of 2–7 sec, preceded the stimulus presentation, but the occurrence of the

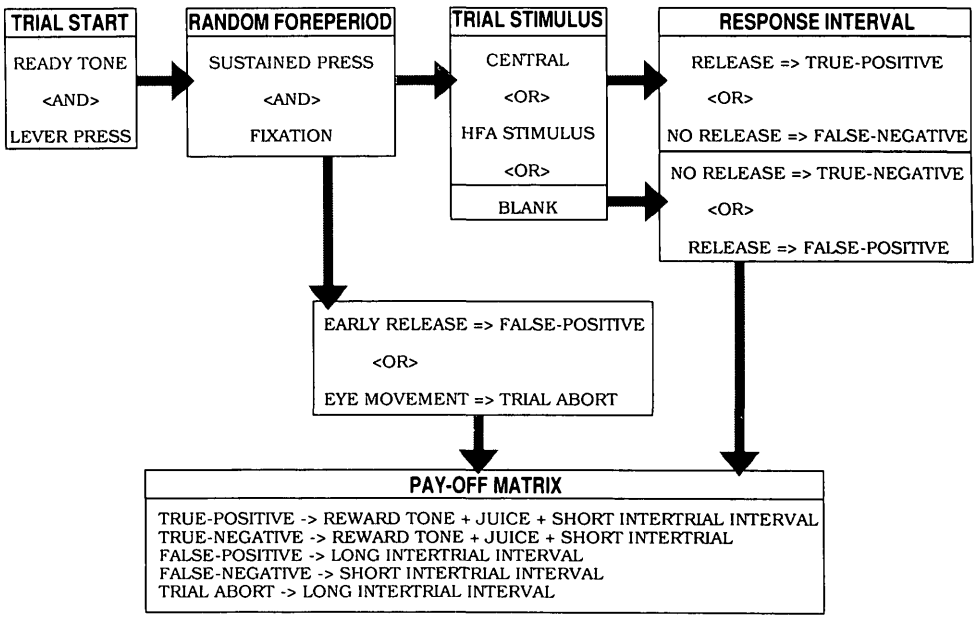

FIGURE 2. Block diagram of the main events of the behavioral procedure. (See text for details.)

stimulus was contingent upon the subject maintaining the lever press and accurate fixation. If either of the incorrect behaviors occurred—ie, a premature lever release or an eye movement away from fixation that exceeded the limit set by the eye movement monitor (4°–5°)—the trial was terminated and an intertrial interval was instituted. In this case, the duration of the intertrial interval was longer than for trials with appropriate behavior (6 versus 1.5 sec). This deterred false alarms, because it delayed the opportunity for an orange juice reward.

With well-trained monkeys, termination of a trial during the fore period (false-positive response) occurred in less than 5% of the trials, and in the usual chain of events, the fore period terminated with the onset of a stimulus interval. The specific stimulus presented in any given trial was one of three types: (1) a luminance increment of the central, fixation stimulus; (2) a luminance increment of a peripheral field stimulus with its location and intensity determined by the specific threshold program of the Humphrey Field Analyzer; or (3) a blank (catch) stimulus. The probabilities for each type of stimulus varied throughout the experimental session. In the first 100 trials of each session, the detection stimuli always were presented at the fixation point to stabilize the monkeys' behavior and to set the sensitivity of the eye movement monitor. When these warm-up trials were completed, the probabilities of the trial types were initialized at $P = 0.3$ for the central stimulus, $P = 0.6$ for a field analyzer trial, and $P = 0.1$ for a blank trial. Subsequently, the probability of the fixation trials was increased by 0.05 after each 100 session trials, with a corresponding decrease in the probability of perimetry trials. The probability of catch trials remained constant.

The variable probability strategy was devised to maintain an approximately constant stimulus detection rate throughout the session. As the session trials proceeded, a larger proportion of the perimetry trials approached their threshold intensity levels, and, as a result, there frequently were long series of consecutive peripheral field trials below the subject's detection threshold. Because such a series of unrewarded trials would weaken the monkey's motivation for the behavioral task, a higher proportion of the trials involved a single field position that had a constant, relatively high detection rate. Across blocks of trials, the luminance increment of the LED fixation stimulus was established by an adaptive staircase designed to maintain a detection rate of approximately 84%.[12]

The basic principle of the behavioral procedure was to establish a form of operant response so highly correlated with the presentation of the detection stimuli that the response inferred stimulus detection by the animal. With our procedure, because the length of the stimulus fore period was not predictable, the stimulus-response correlation was achieved by permitting the monkeys a limited time for executing an appropriate response—the behavioral response interval began 150 msec after stimulus onset and lasted for 750 msec. Within the response interval, a lever release was the conditioned, correct-detection (true-positive) response when a central or peripheral field stimulus had been presented. For a blank trial, a sustained press throughout the response interval was the appropriate correct-rejection (true-negative) response.

To reinforce the monkey's behavior, true-positive and true-negative responses were rewarded. The rewards for these correct responses were a conditioned reinforcer (a 1.6 kHz tone) after each trial and, randomly, an unconditioned reinforcer (0.5 ml of orange juice). The probability of the unconditioned reinforcer was increased throughout the session in an attempt to maintain the monkey's level of motivation through the complete session. Typically, the initial probability of an orange juice reward was set at 0.45 and then increased by 0.03 after each 50 trials in a session.

The alternative responses during the response interval—ie, a failure to release the response lever in a stimulus trial (false-negative) or a release of the lever in a blank trial (false-positive), were not rewarded. False-negative responses simply initiated the short intertrial interval (1.5 sec) that normally separated individual trials. In addition, if the trial stimulus was presented by the perimeter, false-negative responses caused the Humphrey Field Analyzer response switch to be held closed for the entire response interval so the trial response would not be interpreted as a "seen" stimulus by the perimeter's threshold algorithms. On the other hand, false- positive responses invoked the long time-out period (6 sec) that also was associated with false-positive responses during the stimulus fore period.

The visual field data were collected using the Humphrey Field Analyzer C24-1 or C24-2 full-threshold tests. The first measurements were made with the C24-1 program to compare the hills of vision of monkeys and humans along the vertical and horizontal midlines. The later measurements on monkeys were made with the C24-2 program as baseline data for investigations of experimentally induced field changes. For the purposes of the present study, because the primary data analysis involved the perimetry reliability indices, Statpac global indices, and mean threshold across field locations, the two threshold programs should be equivalent.

The results from each session were stored as Humphrey Field Analyzer files. Then, for statistical computations, they were converted to ASCII files for a laboratory PC/IT computer using the Visual Pathways (Davis, CA) data conversion programs. During data

conversion, all of the data for left eyes underwent a mirror-image reversal to put them in a right eye format.

RESULTS

Typical examples of the visual fields of the three monkeys, all collected on the same day, are presented in Figure 3. There is an obvious similarity between these visual field data and the normal visual fields of patients. These data illustrate the effectiveness of the behavioral methodology and also demonstrate the general comparability of monkey and human visual fields.

Perimetry Reliability Indices

For the monkeys, as with human subjects, the best indication that the subject's behavior was appropriate during a visual fields test is when the reliability indices (fixation losses, false-positive errors, false-negative errors, and short-term fluctuation) have low values,[13-14] which permits an inference about the validity of the data. The reliability indices for the monkeys usually were well within the acceptable ranges for clinical data from the Humphrey Field Analyzer. Values for the reliability indices from the visual field data for each of the three monkeys are listed in Table 1 (the data for short-term fluctuation also are presented in

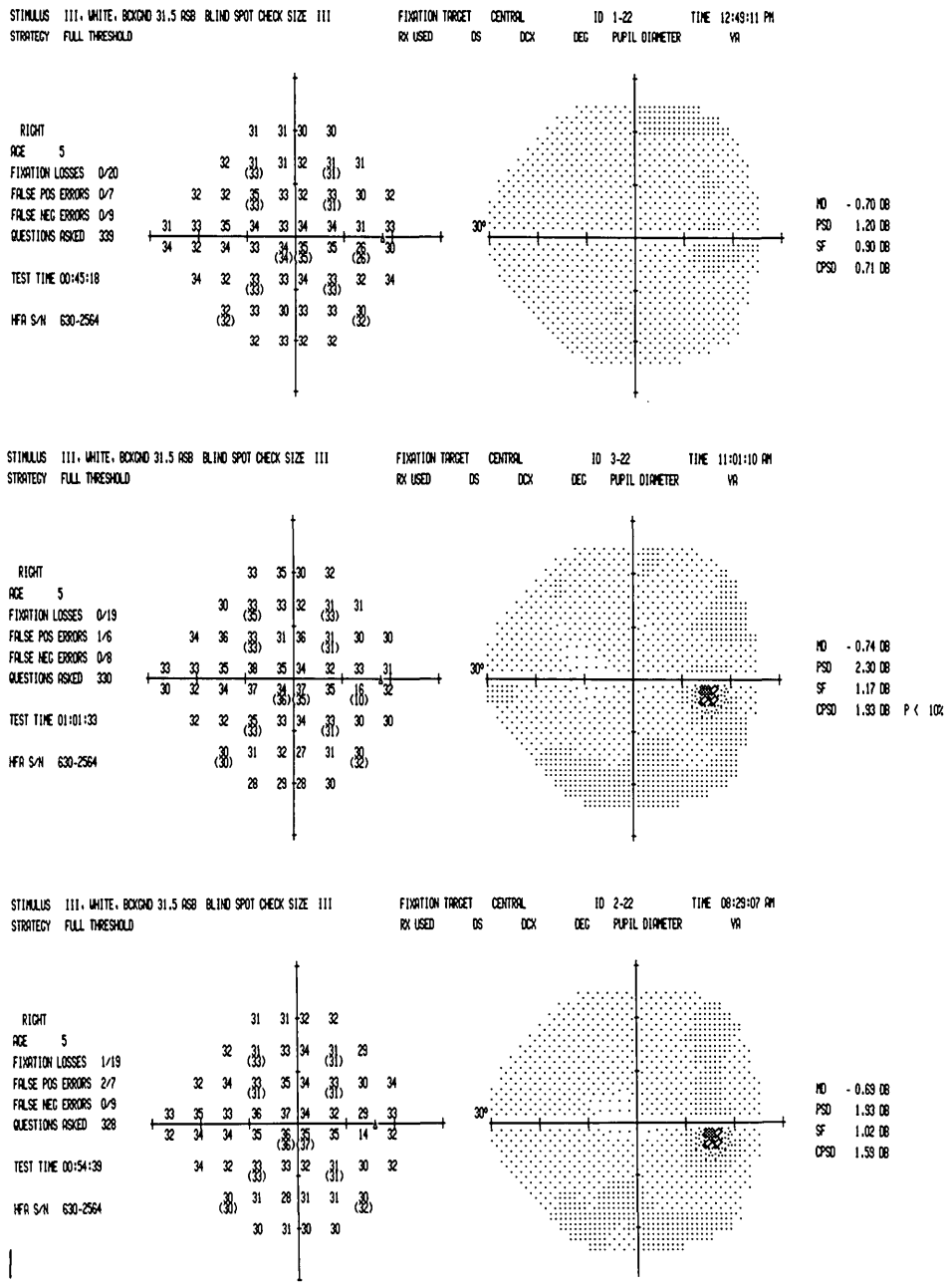

FIGURE 3. Examples of the visual field data for the right eyes of three monkey subjects using the Humphrey Field Analyzer Program C24-2.

TABLE 1. Mean and Standard Deviation Values of the Perimetry Reliability Indices for Monkey and Human Subjects

	Monkeys				*Humans*
Subject	*M-1*	*M-2*	*M-3*	*Mean*	*Mean*
Fixation losses	3.8 ± 0.22%	4.1 ± 0.40%	8.5 ± 0.73%	5.9%	3.8 ± 0.82%
False-positive responses	8.0 ± 0.59%	8.1 ± 0.60%	8.2 ± 0.73%	8.1%	1.2 ± 0.41%
False-negative responses	1.8 ± 0.24%	0%	0%	0.6%	2.6 ± 0.61%
Short-term fluctuation	1.00 ± 0.04 db	1.04 ± 0.06 db	1.09 ± 0.02 db	1.04 db	1.01 ± 0.02 db
Horizontal optic nerve location	16.39° ± 1.13°	15.15° ± 0.87°	15.11° ± 0.57°	15.55°	15.06° ± 0.78°
Vertical optic nerve location	−0.61° ± 0.40°	−1.07° ± 0.47°	−1.00° ± 0.21°	−0.89°	−0.98° ± 0.10°
Mean interocular difference	0.03 db	0.67 db	0.37 db	0.36 db	0.53 db

Figure 4). These values represent the means of 18 measurements for each animal (right eyes) using a Goldmann size III stimulus with the Humphrey C24-2 program. None of the individual values included in the means for any of the monkeys were outside the manufacturer's suggested criteria for data reliability (ie, >20% for fixation losses, false-positive responses, and false-negative responses, or >1.5 db for short-term fluctuation). As also shown by the data in Table 1, the average values of these indices were similar for monkeys and humans; only the percentage of false-positive responses was slightly higher for monkeys than for humans.

The day-to-day consistency of the monkeys' head and eye positions were assessed by the location of the physiologic blind spot. The mean and standard deviation values for the horizontal and vertical positions of the blind spot, shown in Table 1, indicate that the monkeys were consistent in the positioning of their eyes during the field testing. As with the computer reliability indices, there was excellent agreement in the blind spot location for monkey and human observers. It also is noteworthy that these behavioral measurements of the monkeys' blind spot locations reasonably agree with data from physiologic assessments.[15]

The last row of Table 1 presents the average interocular differences for the monkey and human subjects. The data for monkeys represent the differences between the two eyes for the average threshold from all the field locations of the C24-2 program and 18 repeated visual field measurements on each eye. The interocular differences for the eight human subjects were calculated similarly, but with one determination for each eye. As expected for normal, well-trained subjects[16] the intraocular differences were small and of comparable magnitude for both species. As a result, in studies of experimentally induced ocular disorders, an untreated control eye would afford a consistent baseline for nontreatment-related variations in sensitivity.

Visual Field Data

Three types of comparisons of the visual fields of normal monkeys and humans were undertaken: (1) the variation of the visual field threshold values as a function of stimulus field size; (2) the perimetry global indices derived from the Statpac statistical analysis of the data from both species; and (3) a statistical analysis of the variance of threshold values as a function of field location.

Perimetry Thresholds Versus Test Field Area

Visual fields for human and monkey subjects were obtained for the five standard stimulus field sizes of the perimeter, in an unsystematic order, for each of the subjects (three replications per field size for the monkeys and one measure for the humans). The perimetry thresholds were averaged across all field locations to generate threshold-versus-field size functions for the two species (Fig. 4). These functions show a nonlinear, but monotonic decrease in the threshold with increasing stimulus field area—a relationship that also was observed at each of the specific visual field eccentricities. The filled circles, which represent data collected after the monkeys had been working on the task for about 1 month, indicate they were somewhat less sensitive, by approximately 1.6 db, than humans (open circles) for each of the test field sizes. However, when the functions for the monkeys were reassessed, after a longer practice period (filled triangles), they were in excellent agreement with the data for human subjects. This result suggested a protracted practice effect for monkeys, and, consequently, the learning curves for each of the animals were constructed.

Examples of these data for one of the monkeys, with a Goldmann size III stimulus field, are shown in the lower panel of Figure 4. Data for three eccentricities are displayed. The filled symbols represent thresholds, obtained using the C24-1 program, along the horizontal meridian of the nasal field at 6°, 12°, and 24°

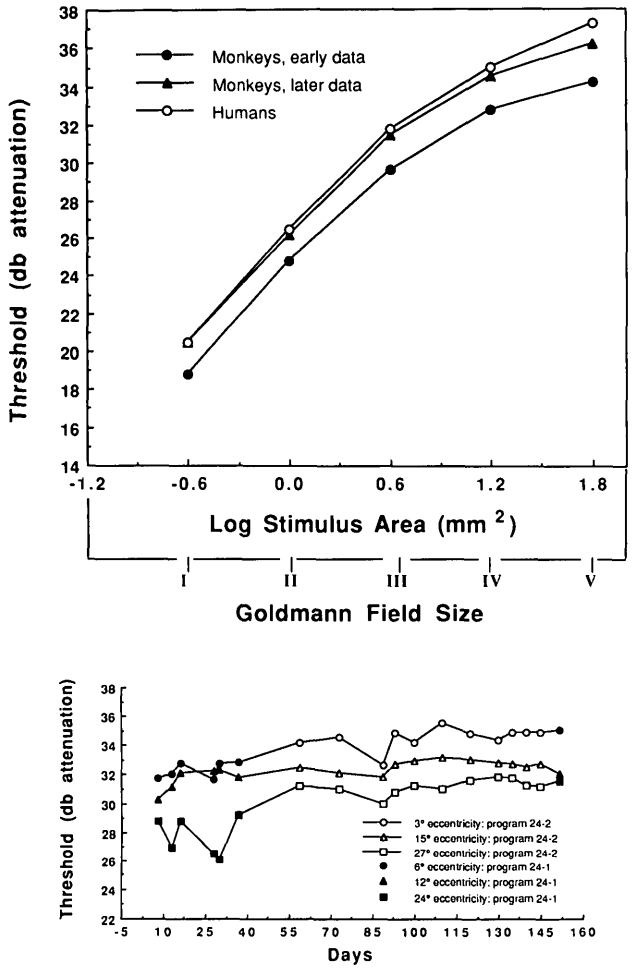

FIGURE 4. Upper panel: Visual sensitivity (decibels attenuation at threshold) as a function of the perimeter test field area for monkey and human observers. The threshold values represent the means of the thresholds for the 54 test field locations of the C24-1 or C24-2 programs using three replications for each of the three monkeys and one measure for each of the eight human subjects. The standard errors of the means (0.2 db for monkeys and 0.15 db for humans) are approximately equal to the symbol sizes for both species. For the monkeys, data obtained after approximately 1 mo (solid circles) and 5 mo (open circles) of training are presented. Lower panel: Learning curves for subject M-1. Threshold values for three eccentricities, indicated by the inset, are shown.

eccentricities. The open symbols represent thresholds with the C24-2 program at similar field locations—ie, 3°, 15°, and 27° eccentricities along the 3° superior, horizontal meridian of the nasal field. The obvious learning effect over the first 90–100 days, especially for the data from the most peripheral eccentricity, fully accounts for the differences in the two threshold-versus-field size functions for the monkeys. Similarly, although such effects have not been specifically demonstrated for perimetry,[17] peripheral vision functions of human observers generally show long-term improvement with practice, especially if feed-back was provided during practice.[18,19] However, the magnitude of these effects usually are smaller for detection than for discrimination thresholds (B. L. Beard, verbal communication, June 10, 1992) and should not interfere with the diagnosis of progressive visual field defects by perimetry.

Perimetry Global Indices

Histograms of the Statpac global indices (mean deviation, pattern standard deviation, and short-term deviation) from 18 measurements for each of the monkeys using the Humphrey Field Analyzer C24-2 threshold program are presented in Figure 5. The means for each of the indices are designated by the dashed lines in the histograms. The mean values for each of the global indices were well within the Statpac range of acceptable variation (95% confidence limits),[20,21] which indicates that the visual field data for average, normal human observers also are an adequate model for the monkey's visual fields. The adequacy of the model is demonstrated by the shape of the hill of vision (pattern standard deviation) and by the height of the hill of vision (mean deviation).

It is interesting that although the mean deviation statistics were not clinically significant, the monkeys were consistently less sensitive than predicted by the Statpac algorithm's empirical model for human vision. One reason for the negative mean deviation values may be related to the analyzer's direct comparison of the chronologic ages of the monkeys and humans. With the monkey's data, the Statpac algorithms performed a linear regression to determine the expected thresholds for a 5-yr-old subject, but the linear regression function may not be appropriate for such young ages. When the monkeys' ages were adjusted by a factor of four,[22,23] the Statpac programs reduced the negative mean deviation index by 1.4 db; thus the mean deviations for all three monkeys were nearly zero. Therefore, the perimetry global indices indicate that the visual field data of normal humans is an appropriate model for normal macaque monkeys, but the data for monkeys should be adjusted for age differences between the two species.

Equality of Means and Variances

The final evaluation of the perimetry data was through a SAS two-way analysis of variance test of the equality of threshold means (Scheffe's multiple comparisons procedure[24]) and a test for the equality of threshold variance (Levene's test for homogeneity of variances[25]). A statistical significance level of $p < 0.05$ was set for all variables. Figure 6 presents the mean thresholds (upper value) and standard deviations (lower value) for each of the field locations that was tested with the Humphrey Field Analyzer C24-2 program.

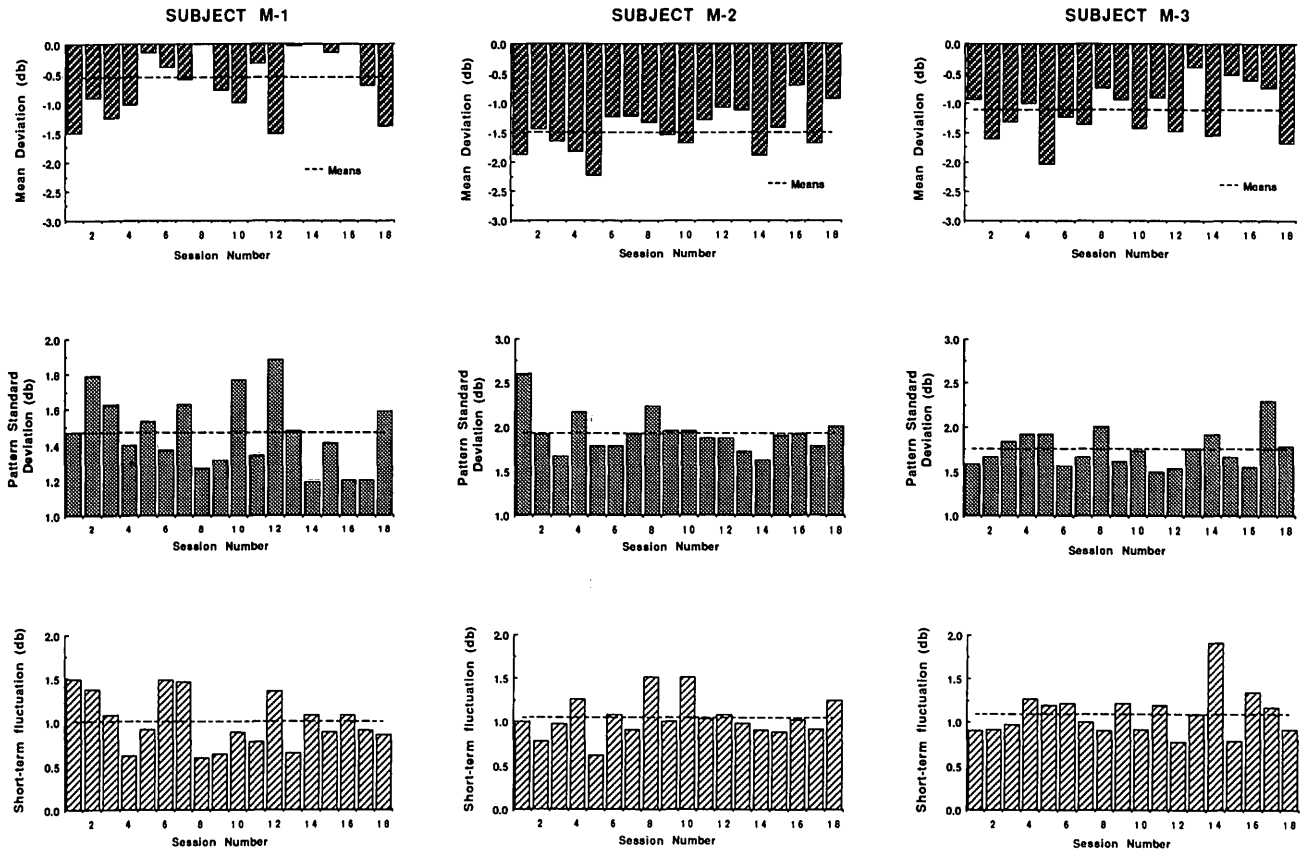

FIGURE 5. The perimetry global indices, derived by the Statpac analysis, across 18 consecutive measurements using the Humphrey Field Analyzer's C24-2 full-threshold program. Mean values for each of the indices are indicated by the horizontal dashed lines.

The data associated with the field locations at 27° in the nasal field (which were not tested in the opposite hemi-field) and the two highly variable points close to the blind spot in the temporal field were eliminated from the statistical analysis. Overall, neither the differences in visual field thresholds nor the variances in thresholds between the individual monkeys were significant. Interestingly, the sensitivities for the monkeys' nasal visual hemi-fields were significantly higher (higher decibels attenuation) than their temporal

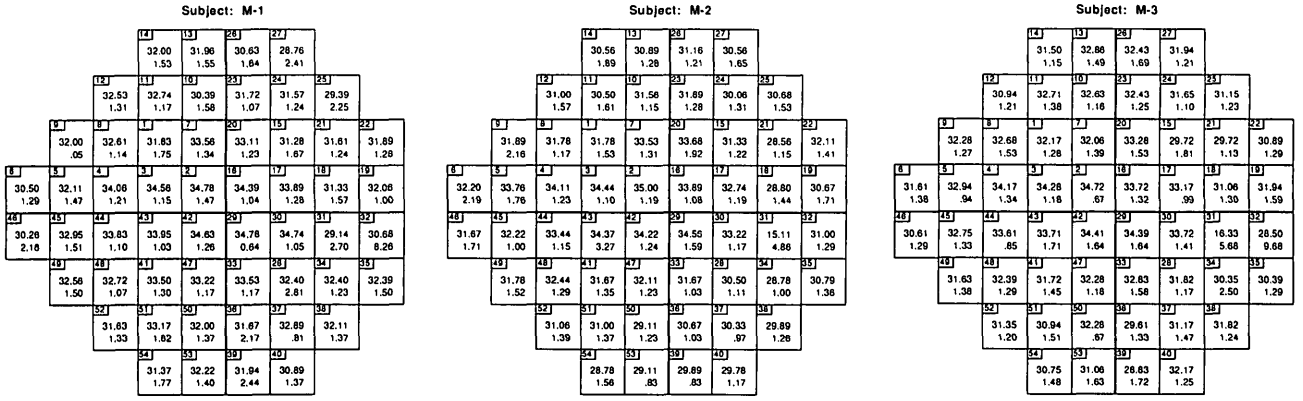

FIGURE 6. Mean thresholds (upper number) and standard deviations of the means (lower number) for each of the test field locations of the Humphrey Field Analyzer's C24-2 program. The data were derived from 18 consecutive measurements from the subjects' right eyes with the standard test stimulus (Goldmann size III). The small numbers in the upper left-hand corners of the boxes around the data entries represent the perimeter manufacturer's designations of field locations.

hemi-fields (mean difference = 0.81 db), but the sensitivities for their superior visual hemi-fields were not significantly different from their inferior hemi-fields (mean difference = 0.18 db).

The mechanisms that underlie the slightly higher sensitivity of the nasal hemi-field are not yet known and, in fact, do not agree with nasal-temporal asymmetries in cone density[26] or ganglion cell density.[15] In addition, the human subjects of the present study did not demonstrate significant differences between nasal and temporal hemi-field sensitivities. However, differences in perimetric hemi-field sensitivities have been suggested by other investigators, but they found lower, rather than higher, sensitivity in the nasal hemi-field and only in right-handed female patients[27].

Overall, the variance of thresholds was homogeneous across the visual field, because there were no statistically significant differences in variance as a function of hemi-field or field quadrant. Regarding field location, the analysis of the variance of threshold measures at iso-eccentric points in each quadrant did not manifest significant differences, but the variance increased significantly with increasing eccentricity. The analysis indicated that the variance of thresholds for field locations separated by 6° were not significantly different, but the differences for field locations separated by 12° always reached statistical significance. In general, the variance of the data for the monkeys agreed with data for human subjects[28] in showing that the variability of measured threshold values depended on eccentricity, with significantly greater variability for the more peripheral field locations. In as much as these properties of the visual fields data of monkeys also imply similarity between the two species, they further validate the monkey as a model for quantitative investigations of visual fields.

DISCUSSION

The general objective of the present study—to compare the shapes and sensitivities of the hills of vision of monkeys and humans by behavioral perimetry on macaque monkeys—was accomplished with positive results. The visual field data obtained from monkeys were remarkably similar to those of human observers. The data were highly reliable, as measured by the perimetry reliability indices, and agreed strongly with the normal reference field of human subjects, as described by the perimetry Statpac global indices.

In a sense, the outcome of this project was predictable because of the close agreement between other visual functions of monkeys and humans in previous psychophysical studies.[7-9] However, the data are very important if the macaque monkey is to be used in subsequent studies of perimetry techniques or in studies of animal models of ocular disease. In this respect, these data on the normal fields of monkeys represent the foundation for investigations in which monkeys are the desirable or necessary subjects. For example, the clinical validity of monkey models of retinal diseases, such as experimental glaucoma, and the use of these models in clinical research should be assessed by behavioral perimetry. In addition, some basic investigations of the techniques and procedures of perimetry require intensive data collection and could be conducted better with monkey subjects rather than human subjects. As a specific case, the proposed use of monochromatic test stimuli, especially blue light, to detect alterations associated with early retinal pathology[29-31] could be studied systematically in monkeys.

The utility of behavioral perimetry with monkeys for clinical research may be questioned as being highly artificial, because it represents a large number of repeated measures on a few very well-trained subjects, unlike the clinical situation, where the data must be obtained from limited measures on relatively untrained patients. On the other hand, measurement variability places a limitation on the interpretation of some important clinical data.[28-33] The animal model provides a method of separating the inherent behavioral variability from variability (or functional changes) caused by the disease process. In the monkey, behavioral variability may be minimized through extensive training; in experimental pathologies, it may be minimized by maintaining an untreated control eye or by obtaining extensive pre-treatment baseline data. Therefore, for some experimental questions, psychophysical studies on monkeys are ideal for initially investigating techniques or procedures that can be applied to human clinical populations for final evaluation.

Key Words

animal psychophysics, monkeys, perimetry, visual fields.

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