

Quantifying Adaptation and Fatigue Effects in Frequency Doubling Perimetry

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PURPOSE. The second eye tested in frequency doubling perimetry has higher thresholds (reduced sensitivity) than the first. The authors investigated how this “second-eye effect” evolves over time and studied systematic changes in threshold in the first eye.

METHODS. Thresholds were measured in four subjects for 5° square, 0.5-cyc/deg sine wave gratings counterphase-flickered at 18 Hz, using a “method of a thousand staircases” to track changes in thresholds at 10-second intervals. Stimuli appeared in 1 of 5 interleaved horizontal locations. Subjects adapted binocularly (background, 45 cd/m²) for 5 minutes before performing a 5-minute test with one eye (the “first eye”) followed immediately by the other (the “second eye”). These results were compared with baseline monocular thresholds measured over 3.5 minutes according to a conventional staircase procedure. In addition, two subjects repeated the main experiment with a translucent, rather than opaque, patch.

RESULTS. On average, second-eye thresholds were raised by 6 dB (0.3 log) at the beginning of the test and were reduced to 4 dB toward the end. Little change was observed in the magnitude of the second-eye effect as a function of eccentricity. A significant “first-eye effect” was also observed in which thresholds increased by approximately 2 dB as the first-eye test progressed. Translucent patching largely abolished first- and second-eye effects, indicating neither was the result of fatigue.

CONCLUSIONS. Steady adaptation in both eyes is important for obtaining stable perimetric thresholds. Unless appropriate tests are performed, the effects of adaptation could easily be mistaken for those of fatigue. (*Invest Ophthalmol Vis Sci* 2007;48:943–948) DOI:10.1167/iovs.06-0685

While determining the normative database for the Frequency Doubling Technology (FDT) perimeter (Carl Zeiss Meditec, Dublin CA; Welch Allyn, Skaneateles, NY), Adams et al.¹ found that the average sensitivity in the second eye tested was reduced by approximately 1.2 dB (0.06 log units) relative to the first. Although this was attributed to a dichoptic contrast adaptation effect, subsequent work has suggested that the sensitivity loss results from a delay in light adaptation of the second eye after its opaque occluder is removed.² Although such effects might be minimized with the use of a translucent

occluder,² this cannot be performed with the FDT perimeter because the opaque occluder is part of the instrument itself. A modified form of the FDT perimeter, called the Humphrey Matrix perimeter (Carl Zeiss Meditec; Welch Allyn) has recently become available, with a smaller target size of 5° that allows the sensitivity of the visual field to be sampled at finer spatial intervals. Examination of the normative database for this instrument confirmed that sensitivity in the second eye was reduced (the “second-eye effect”).² However, the improved spatial resolution of the test also showed that this second-eye effect was not equal across the visual field but was slightly greater in the temporal hemifield.

Aspects of the second-eye effect require more detailed study. Methods used in previous studies^{1–3} have only established an average loss in sensitivity across the duration of a test (approximately 5 minutes); hence, it is unclear how the second-eye effect evolves over time and how it might be most effectively minimized. It is also important to examine how thresholds might vary in the first eye. Previous authors have noted a loss in perimetric sensitivity over time,^{4–9} with many attributing this to subject fatigue.^{4,6–9} Methods to quantify this fatigue effect, however, have had limited temporal resolution. Although it has been demonstrated that the adaptational state of the eye is a critical determinant of the second-eye effect,² the role of light adaptation in mediating any progressive loss of sensitivity in the first eye has not been assessed.

In this study, we measured how the second-eye effect changes over time as the second test progresses by using a slightly unusual test method^{10–12} that allowed us to determine sensitivity at various times throughout the test with a resolution of 10 seconds. This type of testing also allowed us to examine changes in threshold over time as the first eye was tested and thereby to examine any effects of subject fatigue. In addition, we performed investigations to determine the role of light adaptation in progressive changes in threshold in the first and second eyes tested.

METHODS

Apparatus

We presented stimuli on a calibrated video monitor system (Visage graphics card; Cambridge Research Systems, Kent, UK) with a frame rate (Diamond Pro 2070SB monitor; Mitsubishi, Tokyo, Japan) of 100 Hz. The monitor subtended 43° by 33° (width by height) at the 50 cm viewing distance. Ambient room illumination was dim, and the background luminance of the monitor was 45 cd/m² (CIE 1931: $x = 0.279$, $y = 0.299$). A chin-rest restrained the subject's head.

Stimuli were 0.5-cyc/deg sine wave grating patches sinusoidally flickered at 18 Hz and oriented at 180°. Patches were 5° square whose centers were horizontally located at -18° (left), -9°, 0°, 9°, or 18° (right) relative to a 0.3°-wide black fixation square in the center of the monitor. We selected these locations to sample the widest range of eccentricities at the given viewing distance. It has been shown previously that the presence of an unpaired half cycle in such stimuli does not lead to a visible low-spatial frequency artifact.¹³ Stimulus contrasts were specified as Michelson contrast and presented in a raised cosine window of 600 milliseconds.

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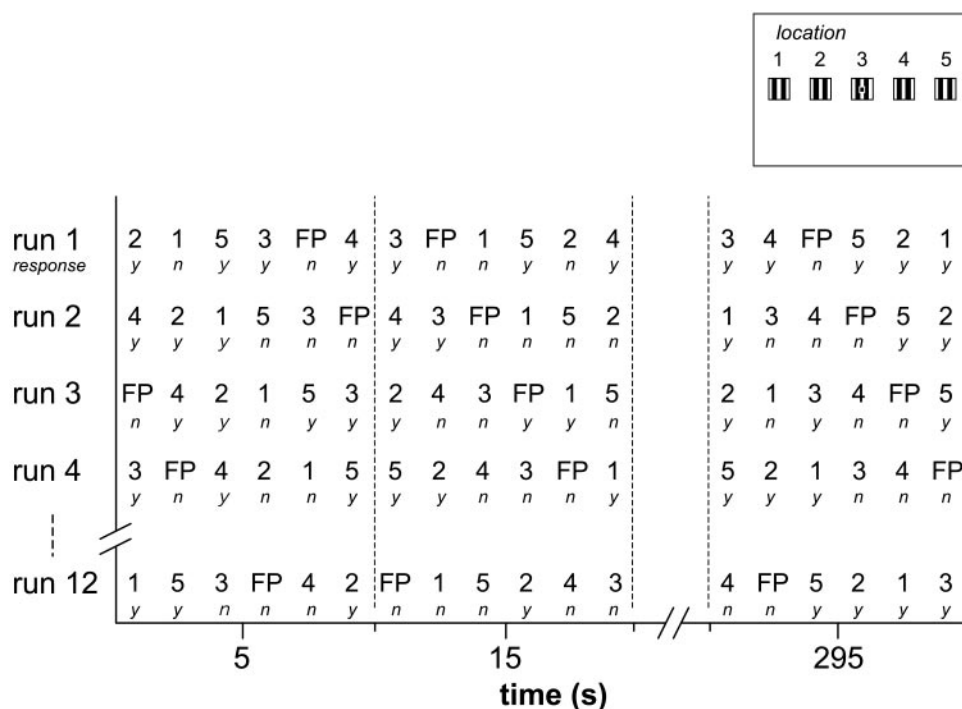


FIGURE 1. Schematic example of the mt-ZEST, a modified version of the conventional ZEST threshold procedure. Numbers in the schematic correspond to the stimulus locations shown in the diagram in the top right corner, with FP denoting a false-positive stimulus. In mt-ZEST, a conventional ZEST procedure is run across tests so that a subject's first response to a target appearing x seconds from the beginning of a test is given in run 1, his or her second response is given in run 2, and so on. For example, the series of responses used to determine the threshold for stimulus 1 at 5 seconds into the test would be n, y, n, n, \dots, y . On each run, the order of the targets was systematically varied to ensure that, on average over the 12 runs, each target was presented exactly at one of the nominal sampling times (5, 15, 25, \dots , 295 seconds).

Thresholding Technique

Bayesian adaptive procedures¹⁴ are among the most efficient for estimating thresholds. Unfortunately, they assume thresholds are constant from trial to trial¹⁵; therefore, such procedures must be modified to measure thresholds that change over time. We modified a ZEST (Zippy Estimation by Sequential Testing) Bayesian adaptive procedure¹⁶ along lines similar to those seen in the "method of a thousand staircases" used to measure rapid changes in light adaptation.¹¹ For convenience, we have denoted our modified procedure mt-ZEST (method of a thousand ZESTs). In brief, our technique involves performing multiple runs of a perimetric test and performing the thresholding procedure across tests for targets at a fixed time relative to the beginning of each run. An important assumption of the mt-ZEST is that a subject's visual system is in the same adaptational state at the beginning of each run, so we ensured that each run was preceded by 5 minutes of binocular light adaptation to the monitor's background luminance. Without such light adaptation, it is possible that thresholds can systematically alter with successive test runs.¹⁷ A more detailed description of our mt-ZEST is given in Figure 1. We presented targets every 1.67 seconds, beginning 0.83 seconds after the beginning of the test, with observers having 1.2 seconds in which to respond by means of a button push; this allowed us to measure thresholds every 10 seconds. A similar technique has previously been applied to the ZEST method to allow it to measure dark-adaptation curves.¹² Our mt-ZEST technique is essentially the same as the original method of a thousand staircases^{10,11} save for the use of a ZEST procedure rather than a staircase logic to determine threshold.

We used a 12-presentation yes-no mt-ZEST procedure, therefore requiring subjects to perform 12 runs of each perimetric test. The procedure converged at the 71% correct level and had a 4 log unit-wide rectangular prior probability density function (prior pdf) to ensure that the pdf did not dominate the final threshold estimate.¹⁴ The midpoint of the prior pdf was centered on a contrast of 5%, and the maximum presentable contrast was limited to 90%. We expressed final threshold estimates in decibels (dB), as given by the equation:

$$\text{dB} = 20 \log_{10} \frac{C}{100} \quad (1)$$

where C is the threshold contrast, expressed as a percentage. Therefore, a change of 20 dB indicates a 10-fold (1 log unit) change in contrast.

Subjects

For experiments 1 and 2, we tested four experienced observers, aged 34 through 46, with corrected visual acuities of 6/6 or better and no history of eye disease. Two of these subjects (the authors) were also tested for experiment 3. All subjects had normal visual fields (pattern SD [PSD] and mean deviation [MD] >5%) as measured on the Humphrey Matrix 24-2 test. Subjects wore their habitual spectacle correction during testing. The study complied with the tenets of the Declaration of Helsinki and was approved by the authors' institutional human experimentation committee, with all subjects giving informed consent before participation.

Procedures

Our study consisted of three principal experiments.

Experiment 1: Quantifying the Second-Eye Effect. Subjects light adapted binocularly for 5 minutes before having one eye opaquely patched (the second eye) and a single run of our mt-ZEST procedure was performed with the other eye (the first eye). On completion, the patch was rapidly swapped, and a single run of the mt-ZEST was performed on the second eye. Subjects repeated the procedure 12 times (see "Thresholding Technique"). The patch was black, close fitting, and opaque.

Experiment 2: Quantifying Light-Adaptation Effects. Subjects light adapted binocularly for 5 minutes before having the second eye opaquely patched and the first eye continued to be adapted for another 5 minutes. The patch was then rapidly swapped, and a single run of the mt-ZEST was performed on the second eye. Subjects repeated the procedure 12 times.

Experiment 3: Influence of Translucent Occlusion. This experiment was identical to experiment 1 except for the use of a translucent patch constructed from dual-thickness adhesive tape (Transpore; 3M Company, St. Paul, MN). Such a patch has been shown to decrease screen luminance by 0.2 log units and to elevate thresholds for conventional FDT targets by more than 26 dB (1.3 log units).² An

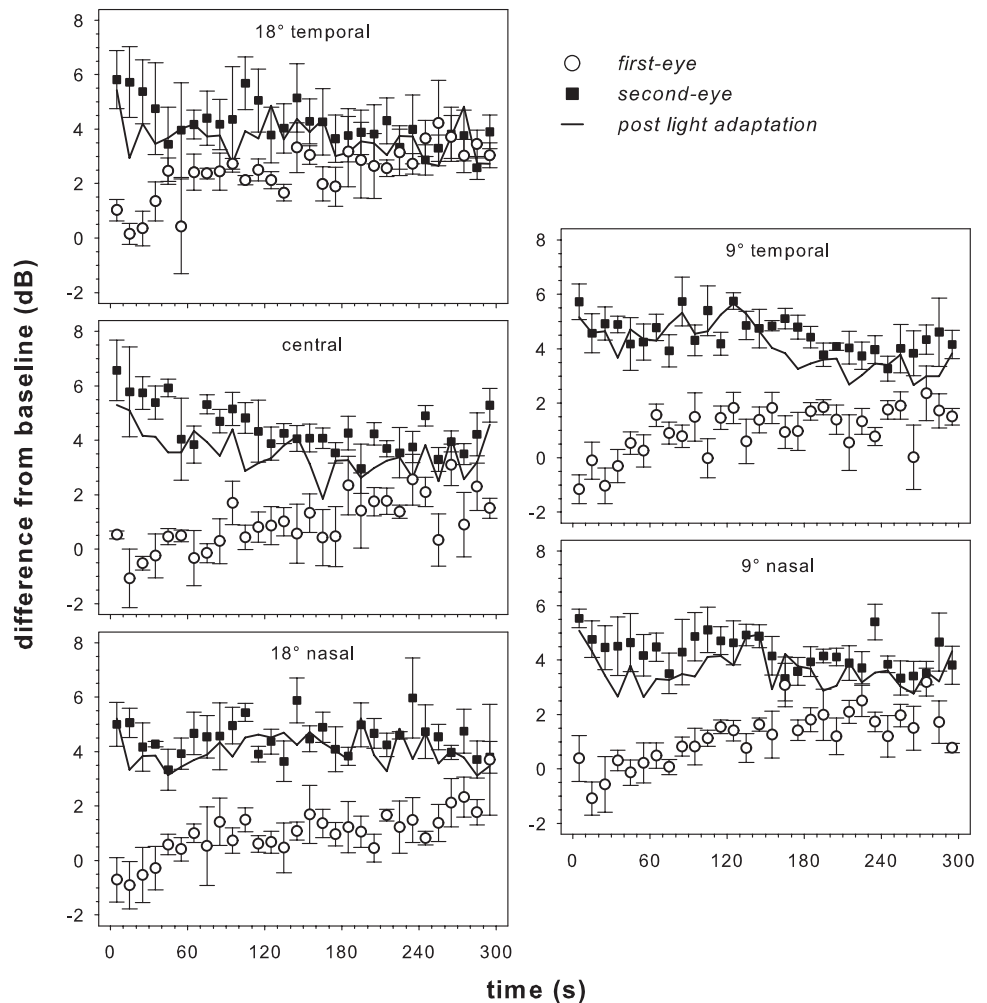


FIGURE 2. Magnitude of the first-eye (○) and second-eye (■) effects as a function of time for five target locations, averaged (\pm SEM) across four observers. Results are expressed as differences from the baseline threshold values returned from a conventional ZEST procedure, with positive dB values indicating a threshold elevation relative to conventional thresholds. *Solid lines* give the effect of monocular light adaptation on second-eye thresholds: average SEMs for these curves are 1.16, 0.62, 0.81, 0.61, and 0.81 (temporal through nasal). A significant ($P < 0.0001$), common linear regression slope of 0.48 dB/min suitably fit the data for the first eye ($R^2 = 0.54$). Slopes for the second eye were -0.37 , -0.22 , -0.37 , -0.21 , and -0.02 dB/min ($R^2 = 0.46, 0.26, 0.39, 0.24, 0.001$) and were significantly different ($P < 0.01$) from zero except for the most nasal point ($P = 0.85$).

even greater threshold elevation would be expected for targets of the type used in the Humphrey Matrix because they are more susceptible to image degradation.¹³ A pilot investigation with the first author as the experimental subject found thresholds could not be measured through the translucent patch.

Experiments 1 and 2, along with conventional threshold determinations, were performed in an interleaved and counterbalanced experimental design. Because of the large amount of time to run these experiments (more than 6 hours per subject), observations were made in half-hour sessions spaced over multiple days. Experiment 3 was performed separately but was also broken into half-hour observation periods over multiple days. For experiments 1 and 2, two subjects used their right eyes as the second eye, with the remaining two using their left eyes. We quantified whether thresholds changed significantly over time by determining whether the linear regression slope for the data differed significantly ($P < 0.05$) from zero. Because these changes were expected to asymptote (see Discussion), it was unlikely that they were truly linear, though it was not unreasonable to think that they were approximately linear over the 5-minute test periods investigated in this study. Consistent with this, the average functions reported in Results showed no significant deviation from linearity (see Fig. 4; runs test on linear regression residuals; $P = 0.17$, $P = 0.17$, and $P = 0.23$ for first eye, second eye, and after light adaptation function, respectively).

Conventional Threshold Determination. In addition to the mt-ZEST procedure described, we determined monocular thresholds after 5-minute binocular light adaptation using a conventional 10-presentation ZEST procedure with 2 interleaved estimates per location, which lasted approximately 3.5 minutes. False-positive presentation rates were 17%. The procedure was run twice, and the final

threshold estimate was taken as the geometric mean of the four individual estimates. Thresholds for right and left eyes were determined after separate periods of binocular light adaptation. We used the same black patch used in experiments 1 and 2.

RESULTS

Figure 2 shows the results for experiments 1 and 2 as a function of the five target positions investigated, with thresholds expressed as a deviation from conventionally determined thresholds (see Methods). Examination of the results of the second eye in experiment 1 (squares) showed a clear initial elevation of thresholds of approximately 6 dB that tended to decrease as the test progressed, reducing to approximately 4 dB by the conclusion of the test. This reduction was significant in all but the most nasal location, with the use of individual slope parameters for each location giving significantly better fits to the data than a common slope parameter (F-test; $P = 0.008$). This second-eye threshold elevation was similar to that resulting from 5 minutes of monocular light adaptation in the fellow eye (solid lines), as investigated in experiment 2. Examination of the first-eye results (circles) showed that thresholds did not remain constant for the duration of the test; rather, they increased significantly by approximately 2 dB. These data could be suitably fit by linear regression curves with a common slope (F-test; $P = 0.74$).

Figure 3 examines the overall magnitude of the first- and second-eye effects by averaging the differences shown in Fig-

ure 2. No significant variation was observed in the second-eye effect (squares) across the eccentricities examined (repeated measures ANOVA; $P = 0.92$). Similarly, no significant variation across the data for the first-eye (circles; $P = 0.053$), despite a larger average difference for the most temporal location. Reanalysis of these functions based on left versus right—rather than on nasal versus temporal—hemifields did not alter the results ($P = 0.38$ first eye; $P = 0.45$, second eye). Because there was little change in effect magnitude as a function of eccentricity for our subjects, we pooled the data from Figure 2 to generate the largely monotonic average functions shown in Figure 4. For these average functions, a total of 12, 11, and 18 false-positive responses were recorded in the first-eye, second-eye, and light-adaptation experiments, respectively, giving average false-positive rates of 10%, 9%, and 15%: the largest and smallest of these rates did not significantly differ (Fisher Exact test; $P = 0.23$) suggesting that there were no gross shifts in response criteria between experiments.

Figure 5 shows the result of translucent occlusion on the results from two observers (experiment 3). In the first eye of both observers, the use of a translucent patch significantly altered the slope of the data (F-test; $P < 0.0001$ and $P = 0.006$; subjects A and B) such that the significant increase in threshold during the test when the fellow eye was opaquely patched (squares) did not occur when translucent patching was used (circles). In addition, translucent patching significantly reduced second-eye threshold in both observers (Wilcoxon matched pairs test; $P < 0.0001$ and $P < 0.0001$, subjects A and B), making second-eye thresholds similar to those of the first eye.

DISCUSSION

Our results showed that perimetric thresholds changed significantly over time in the first and second eyes tested. Consistent with previous results,² threshold elevation in the second eye cannot be explained by a dichoptic contrast-adaptation effect¹⁸ arising from the test of the first eye because a similar elevation was seen when the first-eye test was replaced by 5 minutes of

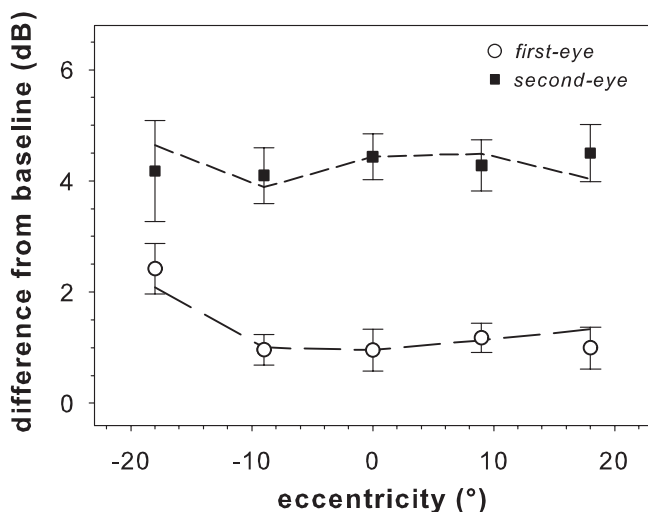


FIGURE 3. Overall magnitude of the first-eye (○) and second-eye (■) effects as a function of eccentricity. This was calculated by first generating curves of the type shown in Figure 2 for each subject and then separately averaging the data in these curves for the first- and second-eye conditions at each eccentricity. Data points represent the mean (\pm SEM) of these summarized data from the four subjects, with negative eccentricities being temporal. Data were also reanalyzed based on target laterality (left = -ve), with the results given by the dashed lines.

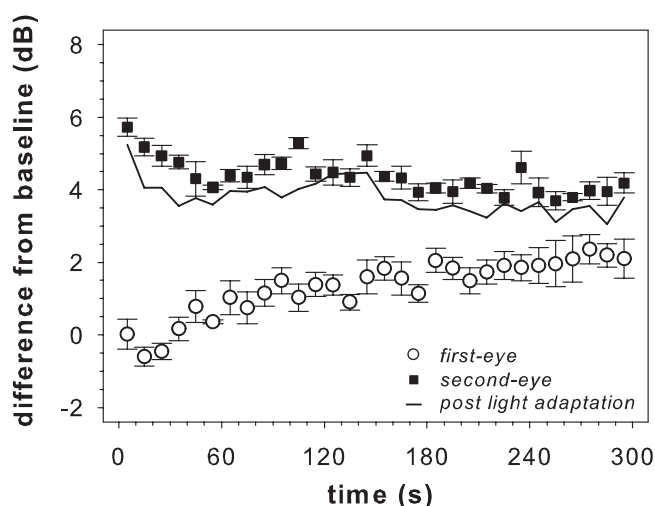


FIGURE 4. Magnitude of the first-eye (○) and second-eye (■) effects as a function of time, averaged (\pm SEM) across four observers and the five target locations. The solid line gives the effect of monocular light adaptation on second-eye thresholds, with the average SEM for this line being 0.28. Positive dB values represent an elevation of threshold relative to baseline thresholds measured by a conventional ZEST procedure. Linear regression slopes (dB/min) for the functions are 0.48, -0.24, and -0.19 (first-eye, second-eye, and post-light adaptation, respectively). All slopes differed significantly from zero ($P < 0.001$).

monocular light adaptation (Figs. 2, 4, solid line). Our results are also inconsistent with changes over time arising from the effects of fatigue. First, thresholds in the second eye were elevated even when subjects did not have to perform a test with their first eye (Fig. 2, solid line). Second, the threshold elevation seen in the second eye significantly decreased over time (Fig. 4, squares), whereas the effects of fatigue should have increased thresholds over time. Finally, use of a translucent occluder abolished the progressive elevation in threshold over time in the first eye (Fig. 5), whereas it would not be expected that the form of occlusion used should influence a true fatigue effect.

Our results show that maintaining a steady adaptation level in both eyes is important for keeping visual thresholds stable over time. Previous research has found that a number of visual functions are impaired when the adaptation state differs between eyes (e.g., dark-adaptation thresholds,¹⁹ visual acuity,²⁰ and perimetric thresholds^{21,22}), and this is thought to result from the effects of binocular rivalry or suppression.²³ Previous work on the second-eye effect in perimetry² could not distinguish between a threshold elevation caused directly by a change in retinal adaptation and one mediated through binocular suppression. Our current results offer more conclusive support of the idea that interocular effects are involved in the effects we report. Our first-eye effect cannot result from a local change in retinal adaptation because the adaptation level in the eye remains constant throughout the test. Rather, the elevation in threshold must result from the increasing difference in adaptation states between eyes as the fellow eye progressively dark adapts under the opaque occluder. Therefore, the locus of sensitivity suppression cannot be retinal, though the signal for suppression probably arises from the difference between a local, retinal adaptation signal from either eye. Consistent with this, Bolanowski²⁴ has shown that the frequency of Ganzfeld blackout increases as the luminance difference between the eyes increases. More recently, it has been shown that postretinal mechanisms are responsive to the background luminance level at the eye.²⁵ It possible that these mechanisms are perturbed in disease; previous work has found that perimetric

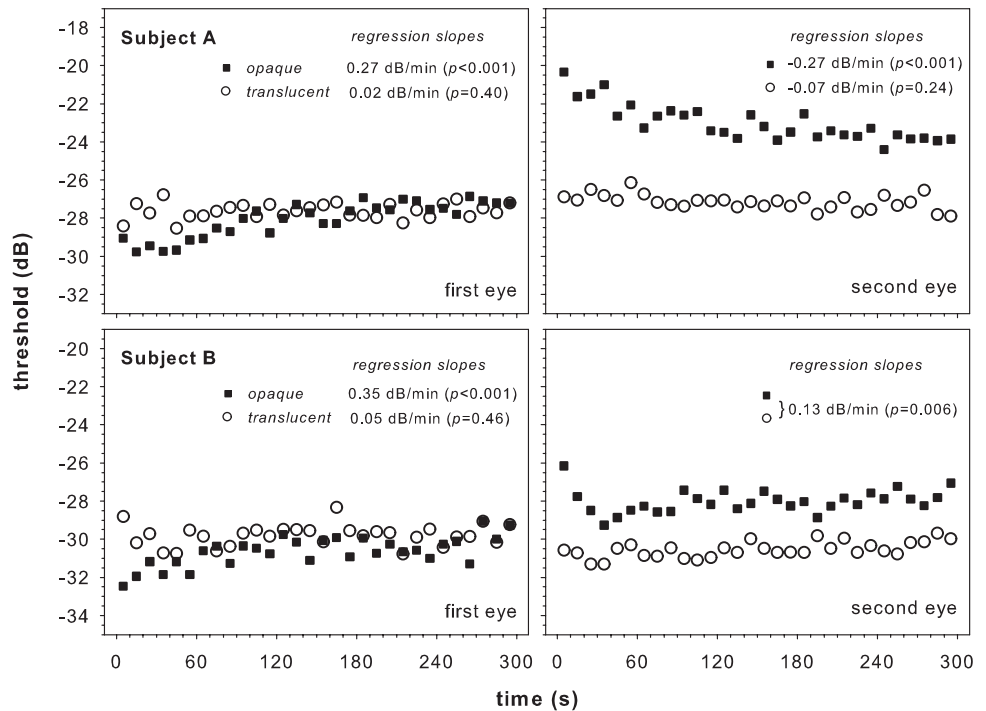


FIGURE 5. First-eye (left) and second-eye (right) thresholds over time using opaque (■) or translucent (○) occlusion of the fellow eye, averaged across the five target locations. For both observers, the use of a translucent patch significantly reduced the regression slopes for the first eye data (F-test; $P < 0.0001$ [subject A] and $P = 0.0063$ [subject B]) and significantly reduced thresholds in the second eye (Wilcoxon matched pairs test; $P < 0.0001$ and $P < 0.0001$). Regression slopes for the second eye differed significantly for subject A but not for subject B (F-test; $P < 0.0001$ and $P = 0.36$).

thresholds change more profoundly over time in glaucomatous visual fields.^{4,26}

As the local adaptation state in the second eye changes while its thresholds are measured, we cannot be as confident that our second-eye effect is the result of binocular suppression rather than a direct effect of light adaptation. It seems parsimonious, however, to invoke the same mechanism for the second-eye effect as is conclusively demonstrated for the first-eye effect. Given the assumption that the binocular suppression mechanism depends on the difference in adaptation states between eyes, one would predict that the average functions presented in Figure 4 should ultimately reach a common plateau when the nontested eye becomes fully dark adapted and the eye under test has reached a stable light adaptation level. Because changes in threshold over time in the second eye likely represent a balance between local and interocular factors, it is more difficult to directly interpret the regression slopes for these data and to know whether the significant differences in slope we found (Fig. 2, squares) are important. Regardless of this potential uncertainty in slope, we show a robust finding that second-eye thresholds are consistently elevated relative to baseline (Figs. 2–5) and that this elevation persists at least as long as the test duration examined here. Indeed, it is likely to persist as long as an adaptation difference exists between the two eyes.

It is worth considering how our results may relate to other common perimetric strategies, such as standard achromatic perimetry (SAP) and short-wavelength automated perimetry (SWAP). The 10-cd/m² background luminance in SAP²⁷ is lower than that used in this study, and it may be thought that the potential for adaptation differences between the eyes is slightly reduced. Significant rivalry effects have been documented in the past, however,²¹ and neither change in threshold over time²⁶ nor frequency of binocular rivalry²⁴ appears to depend on background luminance. A significant reduction in first-eye sensitivity has also been documented with opaque patching.²² The increment used in SAP may not disrupt rivalry effects as well as the flickering targets,²⁸ though it is unlikely that near-threshold perimetric targets are particularly good at disrupting rivalry. Significant rivalry effects might also be ex-

pected in SWAP²⁹ and might exceed those in SAP given that binocular rivalry appears to suppress color-opponent mechanisms to a greater extent than luminance mechanisms.³⁰ Overall it is hard to predict the absolute magnitude of adaptation effects in various types of perimeters, though it seems likely that all forms of perimetry will show changes in threshold over time and a generalized elevation of thresholds in the second eye if the binocular state of adaptation is not appropriately controlled through translucent patching. Although such patching cannot be used in the Humphrey Matrix, this perimeter maintains a separate normative database for the first and second eyes tested,³ thereby accounting for the difference in sensitivity between the two eyes. Indeed, it is debatable whether using translucent patching is appropriate for perimeters that maintain separate databases for first and second eyes. It is unclear whether the standard Humphrey perimeter maintains such databases, though the suggestion is that it does not.⁵ In addition, it is likely that the normative database for this perimeter was collected using opaque patching and so does not account for the small (0.7 dB) increase in sensitivity found when a translucent patch is used.²¹ The most conservative strategy for conventional perimetry, therefore, would be to use opaque patching but to ensure that patients binocularly adapt between the first- and second-eye tests. In this way, the threshold elevation seen in the second eye will be largely abolished. This strategy, however, makes no allowance for the increased patient comfort and reduced threshold variability seen with translucent patching.²¹

Our findings have important ramifications for the development of new perimetric strategies. Historically, many authors have attributed a loss in perimetric sensitivity over time to fatigue^{6–9} and have argued that perimetric test times should be reduced to improve reliability. No doubt this philosophy has spurred, at least in part, the development of faster test strategies.^{31–33} Our results suggest, however, that fatigue may not be a critical factor in threshold drift over time and that appropriate maintenance of comparable adaptation levels between eyes may be more important. Because of this, the development of ever shorter test procedures may be misguided, especially given the well-established tradeoff between speed and accu-

racy in psychophysical procedures.^{16,34} It is possible that, mistaking adaptation effects for fatigue, we have not given our patients enough credit for their ability to maintain vigilance and concentration throughout perimetric tests of modest duration. Further studies using more clinically representative subjects are warranted.

Our results also provide a means by which the variability in perimetric results may be reduced, thereby improving our ability to detect disease and its progression. Most threshold techniques assume that visual thresholds remain constant from trial to trial,¹⁵ but the presence of a systematic change in thresholds over time when opaque patching is used means that this assumption is violated. Such a violation will increase the variability in individual threshold estimates and, hence, also increase the variability in normative databases for perimetry. The assumption that thresholds remain constant over the test duration is better realized through the use of translucent patching. Hence, databases collected under such conditions should show reduced variability and a corresponding enhanced ability to detect disease.

In summary, our results indicate small, but systematic, effects on perimetric thresholds in both eyes as a function of time. These effects are related to the differences in light adaptation state between eyes that occur with opaque monocular patching and can be largely abolished through the use of a translucent patch. Without performing appropriate tests to control for the state of light adaptation in both eyes, however, these effects might be mistaken for fatigue.

Acknowledgments

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