

# Flicker ERG Responses to Stimuli Parametrically Modulated in Color Space

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**PURPOSE.** To develop methods for recording human electroretinogram (ERG) responses to stimuli that modulate different classes of cones in various ratios, to draw inferences about the combination of cone signals in early retinal processing.

**METHODS.** Subjects viewed large-field temporal modulations presented on a computer-controlled color monitor. A flicker photometric paradigm was used to equate the ERG response elicited by interleaved reference and test modulations. Test modulations were chosen to stimulate the L- and M-cones in various ratios. Results were obtained from color-normal subjects, dichromats, and an anomalous trichromat.

**RESULTS.** Reliable signals were obtained from all subjects to both L- and M-cone-isolating modulations and to intermediate modulations. Signals from color-defective subjects were predominantly determined by the modulation seen by only one cone type, whereas signals from color-normal subjects were sensitive to both L- and M-cone modulations. For most color-normal subjects, the recorded signal was a linear function of the contrasts seen by the L- and M-cones. There was individual variability in how strongly each cone type contributed to the overall signal.

**CONCLUSIONS.** It is straightforward to record signals to color modulations presented on a CRT by using the flicker photometric ERG. For most observers, signals from L- and M-cones combine linearly. The relative contribution of the two cone classes varies across observers, probably because of individual differences in the relative numbers of L- and M-cones. (*Invest Ophthalmol Vis Sci.* 1999;40:2840-2847)

The potentials of the flicker electroretinogram (ERG) originate at multiple sites in the retina. To exploit the ERG to understand the flow of information through the retina or to use it as a diagnostic tool, it is necessary to develop techniques that allow the distinguishing of activity generated at individual sites or in particular pathways. Over the years, many approaches to this problem have been developed and evaluated.<sup>1-7</sup> In this article, we examine flicker ERG responses to stimuli that modulate individual cone classes in various ratios. This allows us to study how signals from different cone classes combine to generate the overall electrical response. We used a novel flicker-photometric paradigm. In this technique, the responses to various test modulations are balanced against the responses generated by an interleaved reference modulation. The use of a photometric technique has the important advantage that signal drift over time does not affect the data.<sup>8</sup> The technique used here also extends previous methods, in that it allows the adaptation to be held constant across different stimulus conditions.

Measurements of flicker ERG spectral sensitivity have been used to infer the magnitude of contribution of signals

from separate cone classes.<sup>9-11</sup> Such an approach rests on the assumption that the signals from separate cone classes contribute linearly to the ERG response. In this article, we describe our basic technique and then use it to analyze how signals from different cone classes are combined. Our data provide an explicit test of the linearity assumption. Preliminary versions of this work have appeared in abstract form.<sup>12,13</sup>

## METHODS

### Apparatus and Procedure

Stimuli were presented on a computer-controlled color monitor (Apple PowerMac 6100; Radius Paintboard Turbo graphics card, 9-bit DAC; Radius, Intellicolor 20-in. color monitor; initial experiments, model 0381; later experiments, model 0461). For all experiments, the stimulus was a spatially uniform field modulated in time. The refresh rate of the monitor was 75 Hz. The experimental control software was written in Matlab (The Mathworks, Natick, MA), using the extensions provided by the high-level Psychophysics Toolbox<sup>14</sup> and low-level VideoToolbox.<sup>15</sup>

Any modulation of light around a mean level can be analyzed in terms of the modulations seen by the L-, M-, and S-cones. The modulations were temporal square waves. The contrast seen by the L-cones is  $C_l = (L_{\max} - L_{\min}) / (L_{\max} + L_{\min})$ , where  $L_{\max}$  is the maximum stimulation of the L-cones, and  $L_{\min}$  is the minimum stimulation. Similar definitions of contrast apply to the M- and S-cones. We used the Smith-Pokorny estimates of the cone spectral sensitivities.<sup>16,17</sup> The three numbers  $C_l$ ,  $C_m$ , and  $C_s$  specify the cone contrasts produced by any square wave modulation. By varying the propor-

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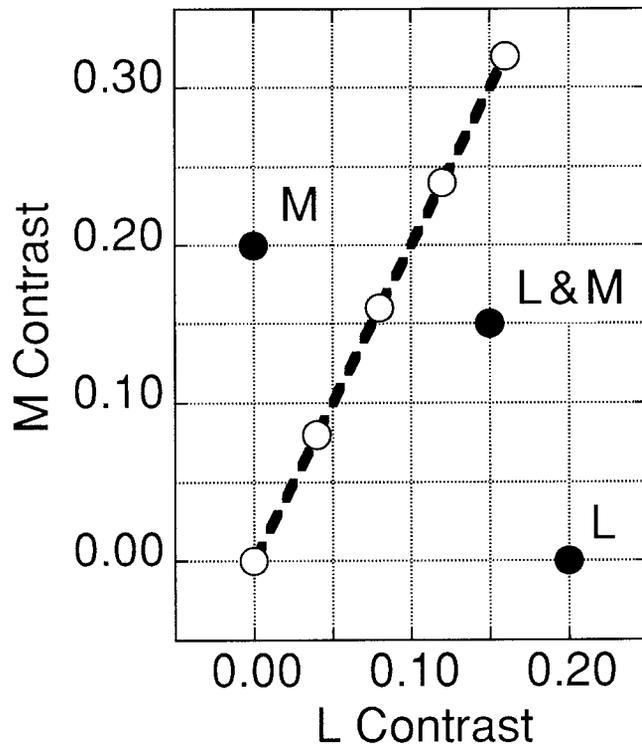
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**FIGURE 1.** Illustration of color space. *Closed circles* show modulations that isolate L-cones, isolate M-cones, and modulate both cone types equally (L & M). *Open circles* connected by a *dashed line* show a series of modulations that share a common ratio of L- to M-cone contrast.

tions of the red, green, and blue phosphors in the two intervals of the square wave, these three contrasts could be varied independently.

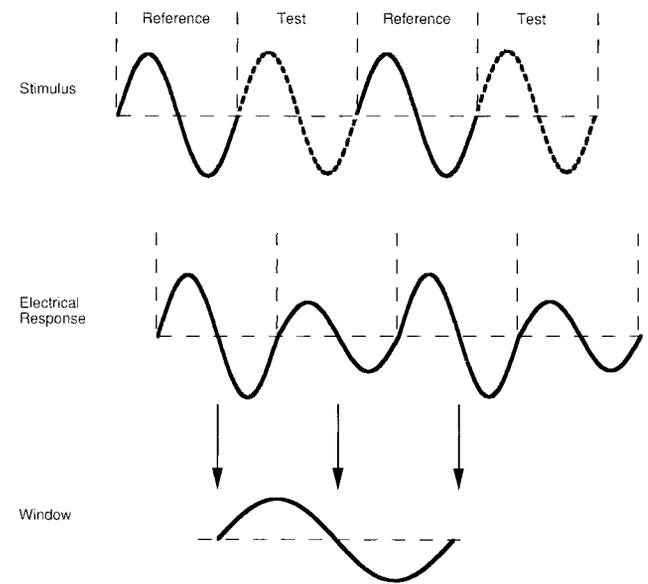
Any modulation can be represented by a point in a three-dimensional cone contrast color space. Figure 1 illustrates this idea for a two-dimensional color space defined by L- and M-cone contrasts, but the generalization is straightforward. The closed circles show three particular modulations. One modulates only the L-cones while holding the M-cone stimulation constant, one modulates only the M-cones while holding the L-cone stimulation constant, and one modulates both cone types with equal contrasts. The open circles connected by the dashed line illustrate a series of modulations, all of which have the same ratio of L- to M-cone contrast. These modulations differ only in the overall contrast seen by the two classes of cone. This group of modulations defines a *direction in color space*.

The top of Figure 2 illustrates the stimulus sequence. The stimulus is a series of interleaved reference and test modulations. The modulations were in different directions in color space. During a single run, the overall contrast of the reference modulation was held fixed. The overall contrast of the test modulation was then varied to equate the signals elicited by the test and reference modulations. This procedure is completely analogous to classic flicker photometry,<sup>18</sup> except that the response to modulations was balanced rather than the response to light increments. An advantage of this approach is that the subject is held in a constant state of chromatic adaptation because the average luminance and chromaticity are independent of the modulation color directions and contrasts.

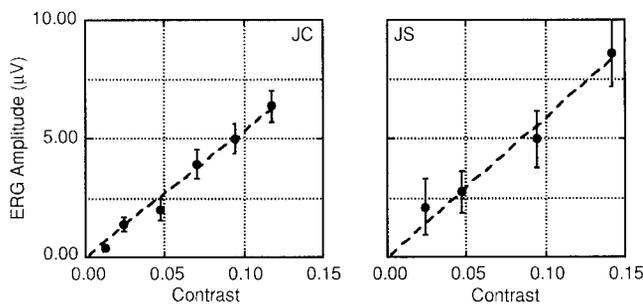
In this sense, our procedure is a physiological analog of heterochromatic-modulation flicker photometry.<sup>19,20</sup>

In all our experiments, the reference modulation was isochromatic, that is, the L-, M-, and S-cone contrasts of the modulation were identical. Typically, these contrasts were set to 8%. For some subjects and test modulation directions, monitor gamut limitations prevented us from finding a test contrast large enough to balance the reference signal. For these, the reference contrast was set to an alternate value (6% or 4%) and the data subsequently corrected. The correction is based on the assumption that the contrast response functions are linear. Over the low contrast range we used, this assumption holds (Fig. 3).

Measurements of the monitor's red, green, and blue phosphor emission spectra and input-output nonlinearities were made using a spectral radiometer (model PR-650; Photo Research, Chatsworth, CA; 380–780 nm, 8 nm full width at half height, 4 nm sampling steps, spectra splined to 5 nm sampling for calculations). These measurements were used together with a standard model of monitor performance<sup>21,22</sup> to determine the digital values required to produce any desired modulation. To correct for small deviations between the model and the real monitor, direct measurements of the experimental modulations were made at the end of each session. These measurements were made either with the spectral radiometer or with a colorimeter (model J-17; Tektronix, Beaverton, OR) equipped with a colorimetric head (model J-1820; Tektronix). In the latter case, we calibrated the colorimeter to our monitor



**FIGURE 2.** Stimulus and response. The stimulus is a series of interleaved reference and test modulations in different color directions. These are shown as *solid* and *dashed* sinusoids in the top row of the figure. The electrical response is shown in the second row. In this example, the test modulation is less effective than the reference modulation. The response is also delayed by a small amount relative to the stimulus. The sinusoidal window shown at the *bottom* of the figure has twice the period of the reference and test modulations, and its temporal phase with respect to the response is as shown. When the electrical response to reference and test modulations has equal amplitude, the windowed response is zero. The actual stimulus was a higher square wave, but the windowing operation filtered out the higher harmonics.



**FIGURE 3.** Contrast response functions for isochromatic modulations (18.75 Hz). Responses were the amplitude of the 18.75-Hz component of the ERG. *Left*, subject JC. *Right*, subject JS. Error bars,  $\pm 2$  SEM.

phosphors by making a one-time comparison between nominal colorimetric values and measurements made with the spectral radiometer.

The space-time average CIE  $xy$  chromaticity was approximately constant across sessions and was 0.27, 0.30, respectively. The monitor's field size and mean luminance were adjustable, and a number of different configurations were used for the experiments reported here. The two field sizes used were 72° horizontal by 72° vertical and 101° horizontal by 85° vertical. The mean luminance varied between 26 and 78 cd/m<sup>2</sup>. Within-subject comparisons across sessions in which field size and mean luminance differed also revealed no substantial effects. Table 1 provides the field size, mean CIE  $xy$  chromaticity, and mean luminance for each subject and session.

### Recording

To maximize retinal illuminance, the pupil of the right eye was dilated by topical application of a mydriatic agent (tropicam-

ide, 0.5%). The left eye was covered by a patch. The subjects were seated in front of the monitor, and the head position was stabilized with the aid of a chin rest. ERGs were differentially recorded using fiber electrodes.<sup>23</sup> The recording apparatus has been described in detail elsewhere.<sup>8</sup>

Analog hardware windowed and averaged (50 window cycles) the amplified signal with a sinusoid of specified spatial frequency and phase. The bottom of Figure 2 shows the relation between the electrical response and the sinusoidal window. Let  $T_s$  be the period of one cycle of the reference or test modulation. The fundamental of the response has this same period. Let  $T_w$  be the period of the sinusoidal window. We set  $T_w = 2T_s$  and the spatial phase of the window so that it had the temporal relation to the response shown in the figure. Thus the windowed response was zero when the raw responses to the reference and test modulations were the same. The experimental procedure was to vary the test modulation contrast until the windowed response was zero. Finding this balance point for a series of color directions yielded a set of modulations that were equally effective at eliciting flicker ERG responses.

### Subjects

There were seven color-normal subjects, one protanope (TF), one protanomalous subject (JD), and two deuteranopes (KA, MS). All subjects were young adults, and all except CB were men. The color-defective subjects were screened according to their performance on standard plate tests (Hardy-Rand-Rittler pseudoisochromatic plates and Ishihara plates). The diagnosis was confirmed by examining Rayleigh color matches (546 + 670 nm = 589 nm), measured with a Maxwellian-view optical system. The details of the procedure used to obtain color matches appeared earlier.<sup>24</sup> For the three dichromats, we subsequently determined the spectral sensitivity of their M/L

**TABLE 1.** Stimulus Conditions and L-M Slopes for Individual Subjects and Sessions

Subject	Color Vision	Field Size	CIE $x$	CIE $y$	Luminance*	LM Slope†
JC	Normal	72° h, 72° v	0.27	0.31	78	-0.69
		72° h, 72° v	0.27	0.30	70	-0.59
		101° h, 85° v	0.27	0.29	25	-1.47
		72° h, 72° v	0.27	0.29	45	-1.13
		101° h, 85° v	0.27	0.30	57	-3.12
AN	Normal	101° h, 85° v	0.26	0.30	56	-0.93
		72° h, 72° v	0.27	0.29	45	-1.21
		101° h, 85° v	0.26	0.29	26	-0.92
BD	Normal	101° h, 85° v	0.28	0.30	57	-1.39
		72° h, 72° v	0.27	0.31	67	-2.51
KK	Normal	101° h, 85° v	0.27	0.29	28	-2.62
		101° h, 85° v	0.27	0.30	28	-2.51
CB	Normal	72° h, 72° v	0.27	0.29	45	-4.41
		101° h, 85° v	0.27	0.30	28	-4.73
JK	Normal	101° h, 85° v	0.26	0.29	28	-47.0
		72° h, 72° v	0.27	0.31	73	
JS	Normal	72° h, 72° v	0.27	0.31	74	
		72° h, 72° v	0.27	0.30	64	
		101° h, 85° v	0.27	0.30	29	
TF	Protanope	101° h, 85° v	0.27	0.30	29	
JD	Protanomalous	72° h, 72° v	0.27	0.30	44	
KA	Deuteranope	101° h, 85° v	0.27	0.30	28	
		101° h, 85° v	0.27	0.30	29	
MS	Deuteranope	101° h, 85° v	0.28	0.30	57	

h, horizontal; v, vertical.

\* Luminance in candelas per square meter.

† Slopes provided where appropriate.

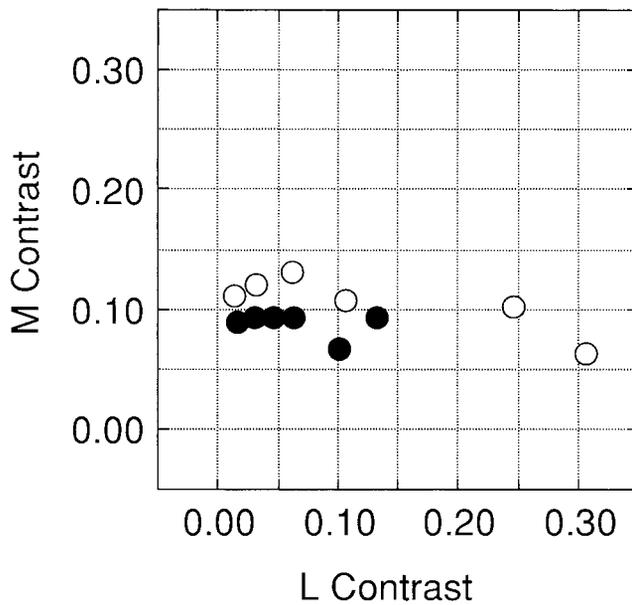


FIGURE 4. Balance data from protan subjects. *Closed circles*, TF (protanope); *open circles*, JA (protanomalous).

cones using ERG flicker photometry. The procedure that was used has been described; it yields a full spectrum for the resident M/L cones.<sup>25,26</sup> The spectral sensitivities for both the deuteranopes and the protanope were typical of those obtained from much larger samples of subjects sharing the respective phenotypes. The peak of the spectral sensitivity function for deuteranope KA was 561 nm, that for deuteranope MS was 563 nm, and that for protanope TF was 531 nm. The ERG flicker photometric procedure also involved a chromatic adaptation test that is used to differentiate between retinas containing one or more than one type of L-M cone.<sup>27</sup> All three dichromats were verified to have only a single class of L-M cone.

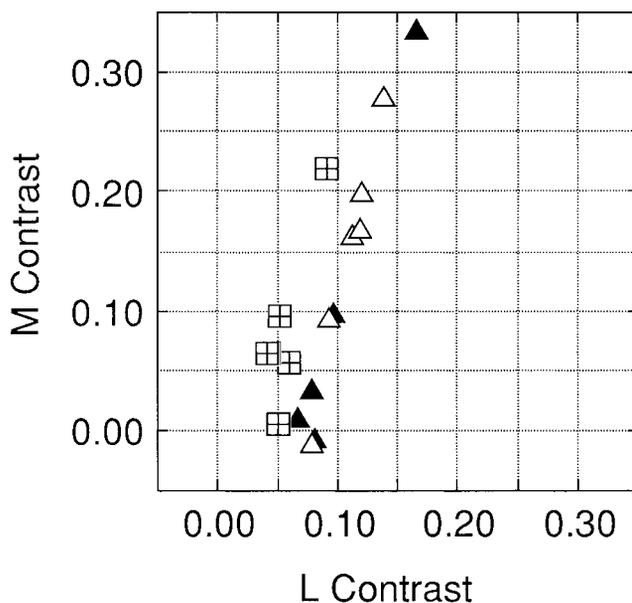


FIGURE 5. Balance data for deuteranopes. *Open and closed triangles* show data for KA from two sessions. *Squares* show data for MS.

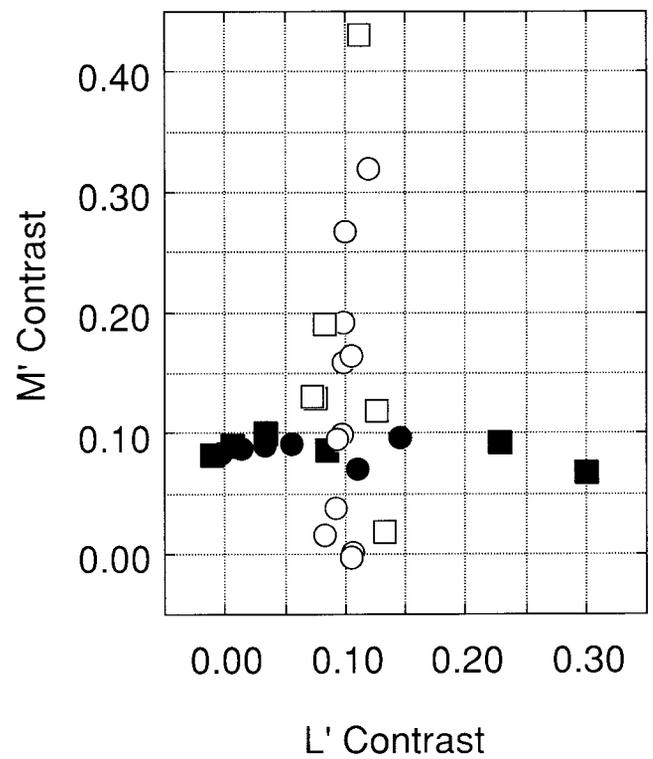


FIGURE 6. Balance data for color-defective subjects in the corrected color space. *Closed symbols* show data from protan subjects: *circles* TF (protanope), *squares* JA (protanomalous). *Open symbols* show data from deuteranopes: *circles* KA, *squares* MS. For clarity, data for JA were scaled to make the mean M' response the same for JA and TF. Data for MS were scaled to make the mean L' response the same for MS and KA. The scaling does not affect the plotted slopes.

The research was approved by the University of California Santa Barbara Human Subjects Committee and adhered to the Declaration of Helsinki.

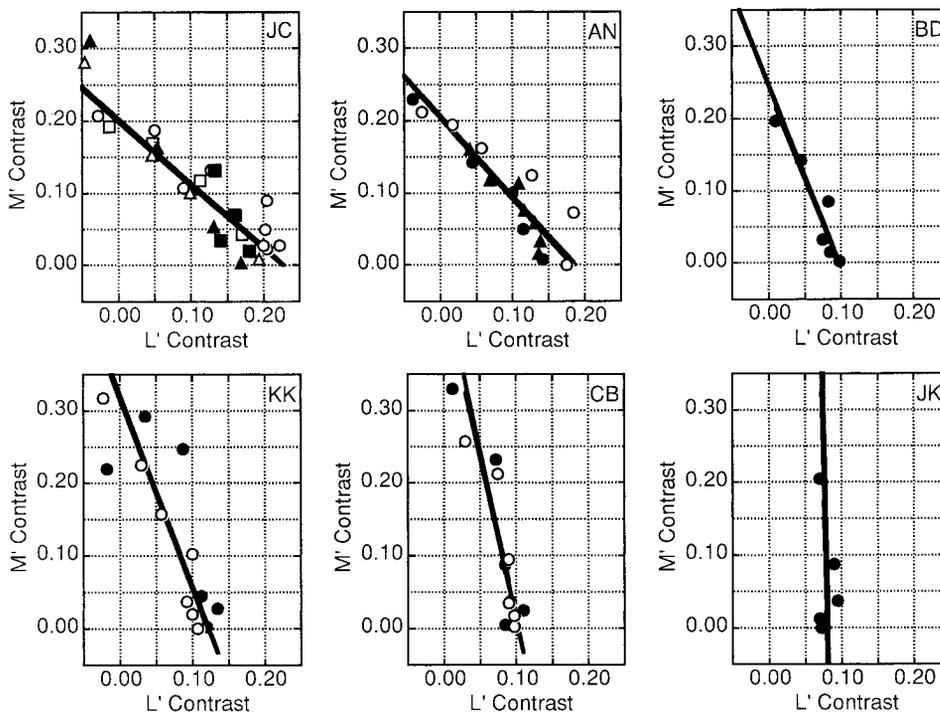
## RESULTS

Signal amplitudes varied somewhat from session to session, but the flicker ERG response to our isochromatic reference modulation (8% contrast, 18.75 Hz) was typically 2 to 3  $\mu\text{V}$  (Fig. 3). In addition, we were reliably able to measure responses for modulations that isolated each class of cone. As an example, for one color-normal subject (JS), an 8% isochromatic modulation was balanced by an 8.2% L-cone modulation, a 12.8% M-cone modulation, and a 50.4% S-cone modulation. These contrasts are based on the Smith-Pokorny cone fundamentals and correspond to 11.0% (L), 11.5% (M), and 50.4% (S) in the corrected color space that we will introduce later in the article.

In this article we focus on results from stimuli that modulated only the L- and M-cones, with the S-cones seeing zero nominal contrast. Postsession calibrations verified that the S-cone contrast was in fact less than 5% for all these conditions.

### L- and M-Cone Phase Differences

The contrasts at which the test modulations just balanced the reference modulation could have been influenced by phase differences in the electrical response to signals originating in different cone classes, irrespective of whether such phase



**FIGURE 7.** Balance data for six color-normal subjects. Initials for each subject are in the *upper right* of the six panels. Separate symbols in each panel indicate data collected in separate sessions. The *solid line* is the best-fitting line to the entire data set. The slope of the best-fitting line for each subject was JC:  $-0.88$ ; AN:  $-1.11$ ; BD:  $-2.51$ ; KK:  $-2.58$ ; CB:  $-4.5$ ; JK:  $-47$ . Data are plotted in the corrected color space.

differences reflected differences in cone physiology or in the postreceptoral pathways. We therefore measured the relative phase of the responses to L- and M-cone-isolating modulations for three of our subjects (18.75 Hz, uncorrected color space). For two of these subjects, there were no reliable phase differences (subject JC: L-cone advance by  $0.4 \pm 1.0$  msec; subject AN: M-cone advance by  $0.9 \pm 0.8$  msec; precision is the SEM). A third subject (JK) showed an M-cone advance of  $5.1 \pm 0.4$  msec. We will return later to a discussion of how small phase differences might reveal themselves in our data.

### Results from Color-Defective Subjects

The closed circles in Figure 4 show the results for protanope TF. Each point in the figure indicates a modulation that exactly balanced the 8% reference. For each test modulation direction, the balance point was obtained when the M-cone contrast was approximately 10%, independent of the L-cone contrast. This was expected, because the protanope had no L-cones. The open circles in the figure show the results for our protanomalous subject (JD). The pattern of the results was the same. Such similarity between dichromats and anomalous trichromats has been observed previously in the flicker ERG.<sup>28</sup>

The open and closed triangles of Figure 5 show the results from two separate sessions for deuteranope KA. The squares show the data for deuteranope MS. Again, each point in the figure indicates a modulation that exactly balanced the 8% reference. The expected result for a deuteranope is that the data would fall along a vertical line, because only L-cone contrast should affect the electrical response. The actual data deviated from this expectation for both subjects. Note that related deviations can also be seen in ERG and psychophysical data collected by others.<sup>28-31</sup> The origin of these deviations is uncertain. Specification of cone-isolating directions in color space is sensitive both to the estimates of cone spectral sensitivity and to limitations in monitor calibration precision, especially for the sharply peaked red phosphor.<sup>32</sup>

The deviations from theory shown in Figure 5 were not large. Because the dichromats had typical spectral sensitivities (described earlier), we elected to use their data to construct the color space in which the remainder of the data were plotted. Let  $L(\lambda)$  and  $M(\lambda)$  be the Smith-Pokorny cone fundamentals, each normalized to a maximum of 1. We constructed new fundamentals  $L'(\lambda)$  and  $M'(\lambda)$  as linear combinations  $L(\lambda)$  and  $M(\lambda)$ , so that the results from the dichromats had the expected form when plotted in comparison with  $L'(\lambda)$  and  $M'(\lambda)$  (see Fig. 6). The required combinations were  $L'(\lambda) = 1.24 L(\lambda) - 0.31 M(\lambda)$  and  $M'(\lambda) = 0.08 L(\lambda) + 0.93 M(\lambda)$ . Note that because the form of the correction was linear, it did not affect conclusions about the linearity of cone signal combination.

### Results from Color-Normal Subjects

Figure 7 shows the results for six of our seven color-normal subjects in the corrected color space. Each panel shows the data for one subject along with the best linear fit (solid line). Data obtained from separate test sessions are shown by different symbols. The following conclusions may be drawn from the figure. First, the data were reliable, as indicated by the correspondence of the results from different test sessions for observers JC, AN, KK, and CB. Second, the data for each subject were well described by a line. This implies that signals from the L- and M-cones contributed additively to the total ERG response. The slope of the best-fitting line (L-M slope) indexed the relative contributions of L- and M-cones to the total response. For example, a slope of  $-5$  implied relative contributions of 5 L to 1 M. Third, there was considerable between-subject variability in the L-M slope. The range was from  $-0.88$  for subject JC to  $-47$  for subject JK. Table 1 provides the L-M slopes obtained from individual sessions for each of these six subjects.

Note that the linearity of the data shown in Figure 7 was not a consequence of the color space correction. This is illus-

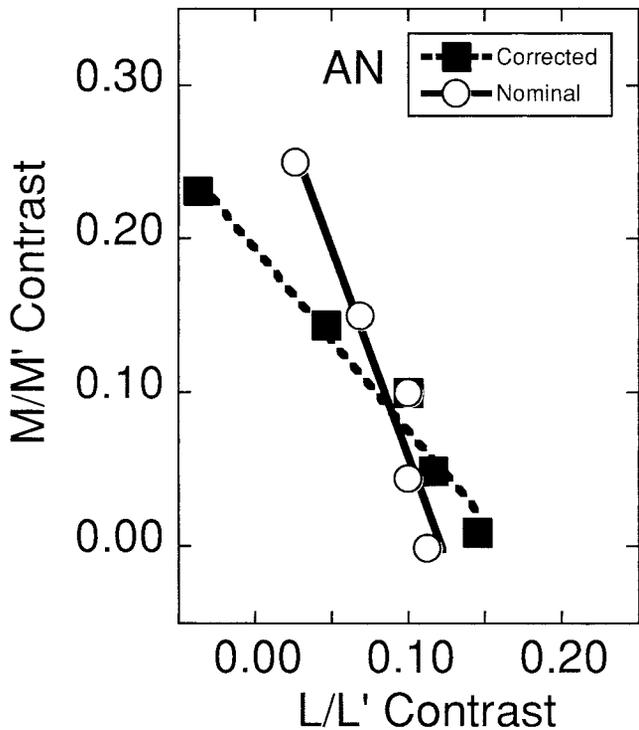


FIGURE 8. Data for a single session for observer AN plotted in the corrected (closed) and uncorrected (open) color spaces.

trated in Figure 8, which shows data from a single session for observer AN. The correction only affected the slope of the best-fitting line; that is, data that are well fit with a line before the correction remained so after it was applied and vice versa.

The seventh subject showed a different pattern of results, as shown in Figure 9. This subject showed a nonadditivity. More contrast was required at balance when L- and M-cones were stimulated together than would be predicted by the additive model. Note that this failure of additivity was replicated across sessions. The nonadditivity could reflect a contribution from an opponent mechanism to the ERG response of this subject.<sup>33,34</sup>

DISCUSSION

The data from six of our seven color-normal subjects were well fit by an additive model. Kremers et al.<sup>31</sup> have also used an additive model to describe flicker ERG data collected using procedures similar to ours. Additivity is consistent with the interpretation that the overall response represents the equally weighted sum of contributions from individual cones in the retina. If this idea is correct, an additive model would describe the data, and the L-M slope would index the ratio of L- to M-cones. Additivity does not contradict the fact that flicker ERG signals have strong postreceptoral contributions.<sup>7</sup> Rather it indicates that the sites from which signals are sampled combine cone signals additively.

A striking feature of our data was the variation in the L-M slope (see Fig. 7). This may reflect individual variation in L-to-M-cone ratio. Although there is abundant evidence for variation in cone ratios, the range we saw was somewhat large compared with that derived from other procedures.<sup>11,35-38</sup>

Note, however, that a similarly large range has been reported by Usui et al.<sup>30</sup> and Kremers et al.,<sup>31</sup> who also studied the L-M slope using the flicker ERG.<sup>30,31</sup> Although it seems likely that true variation in L- to-M-cone ratio would influence the observed L-M slope, other factors may also contribute to the intersubject variation. We now consider several such factors.

The results of the balance procedure were sensitive to differences in phase between the L- and M-cones. As noted earlier, we found only small differences, and these differences varied in size and direction across the subjects. This is consistent with the results of Usui et al.<sup>31,39</sup> who report considerable individual variation in the phase difference between L- and M-cones, ranging from an L-cone advance of 2.8 msec to an M-cone advance of 9.7 msec. Whitmore and Bowmaker<sup>40</sup> report an M-cone advance of approximately 12 msec for a single subject.

To evaluate the influence of an M-cone advance on the L-M slope, we ran numerical simulations. Suppose that the L- and M-cones contribute additively to the flicker ERG and that the L-M slope is -2 if the signals are combined in phase. The lines in Figure 10 show the L-M slope for no M-cone advance (solid, slope -2), a 5-msec advance (dotted line, slope -2.4), and a 10-msec advance (dashed line, slope -5.2). The effect of M-cone advance is to increase the L-M slope, but this increase is modest for advances less than 5 msec. The simulations also indicate that the additive structure of the data are preserved in the face of phase variation—the simulated balance points were colinear for any choice of M-cone advance. In the simulations, we neglected the contribution of S-cones to the response to the 8% contrast isochromatic reference modulation.

Subject JK, who had the most extreme L-M slope, also had the most substantial M-cone advance. Taking his M-cone advance to be 5.1 msec, we determined that in the absence of an advance the measured L-M slope would have been -38.5. At the other extreme, subject JC (measured slope -0.88) showed no phase difference. Once the phase differences are taken into account, the range of L-M slopes is -0.88 to -38.5.

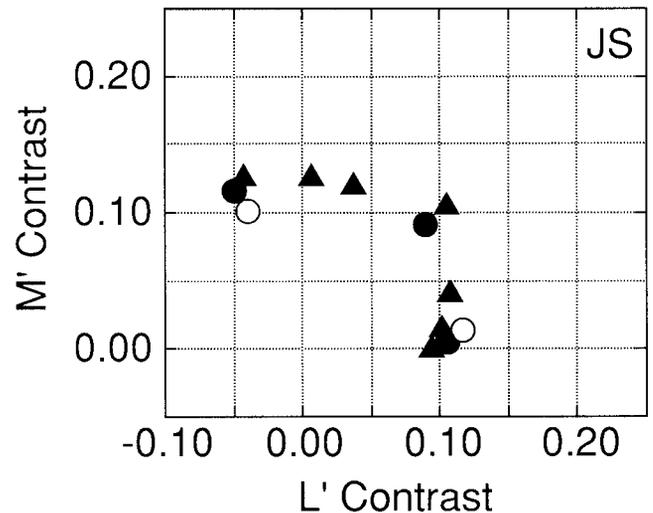
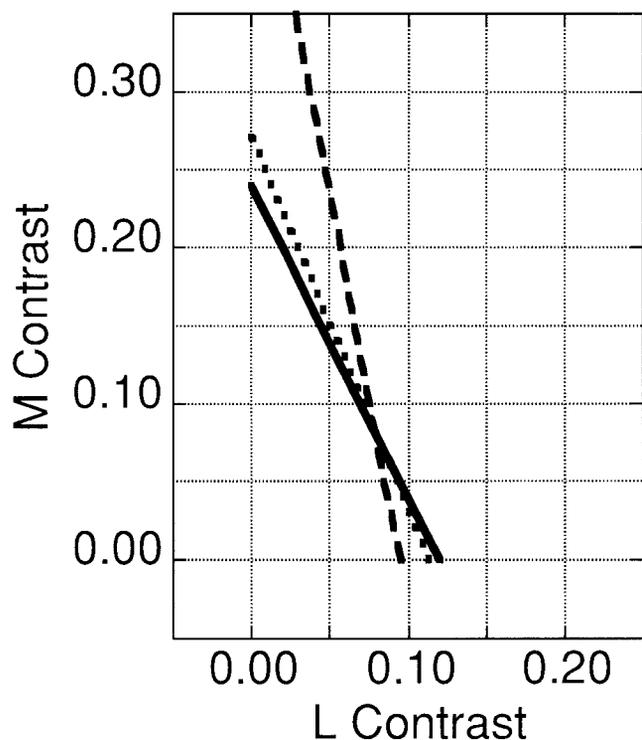


FIGURE 9. Balance data for color-normal subject JS. Separate symbols in each panel indicate data collected in separate sessions. Note that these data are not well fit by a line. Data are plotted in the corrected color space.



**FIGURE 10.** Simulation results. Given an assumed L-M slope of  $-2$  with no L-M phase difference (solid line), the figure indicates the expected L-M slope for a 5-msec M-cone advance (dotted line, slope  $-2.4$ ) and a 10-msec M-cone advance (dashed line, slope  $-5.2$ ).

The interpretation of L-M slope also depends on the assumption that each subject has L- and M-cone photopigments with identical absorption spectra.<sup>41</sup> Contemporary research indicates that this assumption is a simplification, but there is still some disagreement about the range and nature of the variation.<sup>42,43</sup> To assess the effect of such photopigment polymorphism, we computed how the L-M slope varied as the peak of the L-cone photopigment was shifted along the wavelength axis. We assumed that the Smith-Pokorny estimate of the L-cone spectral sensitivity represents a population average and that the total variation in L-cone position is 4 nm.<sup>42</sup> From a starting L-M slope of  $-2.0$ , a shift of  $-2$  nm decreased the slope to  $-2.7$ , whereas a shift of  $+2$  nm increased the slope to  $1.6$ . From a starting L-M slope of  $-38.5$ , a shift of  $-2$  nm decreased the slope to  $-8.4$ , whereas a shift of  $+2$  nm increased the slope to  $15.6$ . Taken with the results of Figure 10, these calculations suggest that neither phase differences nor L-cone photopigment polymorphism can account for all our measured variation.

Other factors could contribute to variation in the L-M slope. For example, individual variation in differential gains on the signals from L- and M-cones to postreceptoral sites would influence the L-M slope. We think it most likely, however, that our results tap intersubject variation in the L-M cone ratio.

In sum, our results suggest that it is straightforward to measure flicker ERG responses to cone-modulating stimuli at contrasts and luminance levels that can be produced on a standard color monitor under conditions in which adaptation is stringently controlled. The measurements support the assumption that the major contribution from L- and M-cones to the flicker ERG is additive, just as it is for spectral

luminosity functions obtained psychophysically with flicker photometry.<sup>44</sup>

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