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Authors

Jacobs, G H
Williams, G A

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L and M cone proportions in polymorphic New World monkeys

GERALD H. JACOBS AND GARY A. WILLIAMS

Neuroscience Research Institute and Department of Psychology, University of California, Santa Barbara, California

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Abstract

Platyrrhine monkeys typically have only a single X-chromosome opsin gene. Alleles of this gene code for multiple versions of middle- to long-wavelength cone photopigments. X-chromosome inactivation provides heterozygous females with a retinal mosaic of cones containing either of two types of M and L pigment, thus establishing the photopigment basis for trichromatic color vision. This study examined the proportions of L and M cones created by this process. For that purpose, electroretinogram flicker photometry was used to obtain complete spectral sensitivity functions from 60 heterozygous female monkeys drawn from seven genera of platyrrhine monkeys. To obtain estimates of cone proportions, these functions were subsequently fit with linear combinations of L and M cone fundamentals that were derived from similar recordings made on conspecific animals having only one type of M/L pigment. Consistent with a random X-chromosome inactivation process, the average L:M cone weighting across the sample was close to unity. At the same time, there were significant individual variations in L:M cone proportions. The genesis of this variation and its implications for seeing are discussed.

Keywords: Platyrrhine monkeys, Cone pigments, Cone proportions, X-chromosome inactivation, ERG

Introduction

Primates are unique among eutherian mammals in having three types of cone photopigment segregated in three classes of cone, typically designated as S, M, and L (short-, middle-, and long-wavelength sensitive). Catarrhine primates show significant species variations in the overall representation of L and M cones in the retina. For instance, a variety of types of measurement show humans to have L:M cone ratios averaging about two (Cicerone & Nerger, 1989; Pokorny et al., 1991; Hagstrom et al., 1998; Bowmaker et al., 2003). At the same time, the L:M ratios in macaque monkeys are lower than those characteristic of humans, somewhere in the range of 1 to 1.5 (Jacobs & Deegan II, 1997; Deeb et al., 2000; Dobkins et al., 2000; Roorda et al., 2001), while in baboon retinas this relationship is reversed with M cones actually outnumbering L cones (Marc & Sperling, 1977; Bowmaker et al., 1983; McMahon et al., 2001). In addition to these average variations across species, there can also be significant individual variations in L:M cone ratios. Such variation has a long history of study in humans (e.g., De Vries, 1948; Rushton & Baker, 1964) with a recent examination concluding that L:M cone ratios vary between 1:3 and 13:1 across individuals (Carroll et al., 2002). These species and individual variations in L and M cone representation are of interest because they can impact various aspects of

visual sensitivity and color vision and because they provide constraints for models of the nature of signal processing in the retina and beyond.

What accounts for the variations in L and M cone representation? The genes specifying the L and M cone opsins of catarrhine primates lie in tandem array on the X chromosome, and it is believed that interactions between an upstream locus control region (LCR) and the promoters of the L and M opsin genes determine which gene gets expressed in a given cone (Wang et al., 1992; Wang et al., 1999; Smallwood et al., 2002; McMahon et al., 2004). Some features of variation in the structure of these components, or of their interactions, are thought then to control the relative numbers of L and M cones, and these features could presumably impact both species and individual variations. Platyrrhine monkeys would seem to present a simpler situation in that most species from this group have only a single X-chromosome opsin gene (Jacobs, 1998). In such monkeys multiple alleles code for spectrally variant forms of the L and M pigments. Unlike the catarrhines, in platyrrhine monkeys X-chromosome inactivation is the prime mechanism for sorting M and L pigments into separate cone types (Mollon et al., 1984; Jacobs & Neitz, 1987). X inactivation is a long-established mechanism for gene dosage compensation in mammals according to which early in female embryological development one of the two X chromosomes is randomly inactivated in each cell and this inactivation is maintained in the subsequent progeny of this precursor cell pool (Lyon, 1961). As a result of this process heterozygous female platyrrhine monkeys achieve separate populations of L and M cones, and from this they

Address correspondence and reprint requests to: Gerald H. Jacobs, Neuroscience Research Institute, University of California, Santa Barbara, CA 93106, USA. E-mail: jacobs@psych.ucsb.edu

can derive trichromatic color vision. It seems reasonable to presume that not only does X inactivation allow heterozygous females an additional dimension of color vision, but that it may also be a major factor in regulating the relative proportions of cones that express the L and M pigment variants in these trichromats. If this correct, and if X-chromosome inactivation is indeed random, the expectation would be that the average L:M ratios in these primates should be close to unity with individual animal variability reflective of the size of the precursor cell pool at the time of inactivation.

To date there is little direct information regarding L:M cone ratios in the polymorphic platyrrhine monkeys. Bowmaker and colleagues used microspectrophotometry (MSP) to identify the cone pigment complements of 50 foveal cones in a trichromatic marmoset (Bowmaker et al., 2003). For this one individual the derived L:M ratio was about 0.7. An earlier analysis of MSP data is consistent with the conclusion that the two L and M cone types are about equally represented in the retinas of four trichromatic squirrel monkeys (Bowmaker et al., 1985). Both of these studies necessarily involved only small numbers of receptors and animals. We have attempted to extend our understanding of L:M cone ratios among the polymorphic platyrrhines by using measurements of spectral sensitivity derived from electroretinogram (ERG) flicker photometry as a tool for deriving estimates of the relative retinal representation of the L and M cone types in trichromatic females.

Materials and methods

Over the past two decades ERG flicker photometry has been used in this laboratory to study cone photopigments and their variations in a substantial number of platyrrhine monkeys. This noninvasive technique allows one to rapidly and reliably measure spectral sensitivity. We have now analyzed results obtained from a subset of these animals to derive estimates of L:M cone ratios in heterozygous females.

The measurement technique has been fully described (Jacobs et al., 1996), as has its application to studying cone-based vision in platyrrhine monkeys (Jacobs & Deegan II, 2003). In brief, ERGs were recorded from sedated monkeys with bipolar contact-lens electrodes. The stimuli were large field (59 deg) diffuse flashes imaged through a dilated pupil onto the retina in Maxwellian view. A flicker photometric procedure was used in which the responses obtained to a monochromatic light flickering at 31.25 Hz were equated to ERGs produced by the presentation of a similarly flickering, interleaved reference light (achromatic, 2450 K; retinal illuminance = 3.3 log td). The responses were averaged over the last 50 of a total of 70 stimulus cycles. Over successive presentations the intensity of the monochromatic light was adjusted until it produced an ERG that exactly matched that for the achromatic light. This photometric equation defines a single point on the spectral sensitivity function. This procedure was repeated for a range of monochromatic test lights that were varied across the spectrum in steps of 10 nm, typically from 440 nm to 650 nm. Equations were obtained twice for each test wavelength during the recording session, and these separate results were subsequently averaged to produce a spectral sensitivity function.

Results were examined for 60 female platyrrhine monkeys, each of which (1) had been shown by results from a chromatic adaptation experiment conducted in the same recording session to have two types of M and L cones in her retina, and (2) had yielded a high quality spectral sensitivity function. These animals were drawn from a range of different polymorphic platyrrhine species including: *Saimiri sp* (squirrel monkeys, $n = 26$), *Ateles sp* (spider

monkeys, $n = 15$), *Cebus sp* (capuchin monkeys, $n = 4$), *Saguinus oedipus* (cotton-top tamarins, $n = 5$), *Leontopithecus rosalia* (golden-lion tamarins, $n = 5$), *Callicebus moloch* (dusky titi, $n = 4$) and *Pithecia pithecia* (white-faced Saki monkey, $n = 1$). All experimental procedures were conducted in accordance with institutional animal care and use guidelines and with the ARVO statement for the Use of Animals in Ophthalmic and Vision Research.

A traditional way to estimate cone ratios is to fit spectral sensitivity functions obtained with flicker photometry with cone fundamentals, assuming that the weighting functions required for such fits provide estimates of the L:M cone ratio (Lennie et al., 1993). This technique has in the past been applied to ERG flicker photometric spectral sensitivity functions obtained from human trichromats (Jacobs & Neitz, 1993; Carroll et al., 2000). Such fits depend on having accurate measurements of the M and L fundamentals. For fundamentals we used the M and L cone pigment positions as obtained from ERG flicker photometric measurements made in dichromatic conspecifics and then captured by standard photopigment absorption functions (Jacobs & Deegan II, 2003). To minimize the influence of any preretinal filtering (which is unknown in detail for most platyrrhines), we followed the strategy of truncating the spectral measurements prior to fitting so as to only include wavelengths of 500 nm and longer (Sharpe et al., 1998). A number of different M and L pigment positions are represented both within and between the species examined (Jacobs, 1998). For all of the monkeys in this sample, the two M/L pigments were peak separated by at least 12 nm. For convenience, we here refer to the shortest of each pair as M and the longest of the pair as L, irrespective of their actual spectral positions. To determine the weighting of the two fundamentals required to best fit the spectral sensitivity functions, the two were varied in steps of 0.1% until the best least-squares fit to the function was obtained. Pigment optical density was a free parameter in this fitting procedure. For these ERG measurements, platyrrhine M/L pigments fitted in this way yield optical density values that are typically < 0.1. Examples of such derived functions are shown below.

Results and discussion

Validity and reliability of the measurements

How valid is this approach as a surrogate for actually counting L and M cones? The most direct evidence that this procedure yields valid estimates of L:M cone ratios comes from studies that compared such ratios obtained from ERG measurements made in this laboratory with receptor counts derived from a direct imaging of the retina using adaptive optics. In one investigation, two human subjects whose L:M weighting functions estimated from ERG spectra were 1.06 and 3.38 had L:M cone ratios of 1.15 and 3.79, respectively (Brainard et al., 2000). A more recent study also reports a very high correlation ($r^2 = 0.98$) between L:M ratios inferred from adaptive optics measurements and from the ERG (Hofer et al., 2005). It thus appears that fitting cone fundamentals to ERG spectra provides a fully legitimate means of estimating L:M cone ratios. The reliability of the ERG measurement could of course be established by making repeated recordings from the same subject and comparing the L:M cone weightings obtained across such experiments. Practical restrictions on the monkey recording experiments made it impossible to obtain repeated measurements on individuals. However, repeated measurements have been made on individual human subjects, and they suggest the technique yields quite reliable estimates of L:M ratios. For exam-

ple, we earlier measured ERG flicker photometric spectral sensitivity functions from a normal human trichromat using techniques equivalent to those used with monkeys. The L:M ratios derived from the three measurements of this subject made over the course of several months were 1.45, 1.68, and 1.51 (unpublished measurements). Repeat flicker photometric ERG measurements made elsewhere on two other human trichromats show variation of similar magnitude (Carroll et al., 2000). We conclude from these validity and reliability checks that ERG flicker photometry provides a reasonable approach to estimating L:M ratios in individual subjects.

L:M cone ratios and their variations in platyrrhine monkeys

Fig. 1 illustrates the spectral sensitivity data from which L:M cone ratios were derived. Shown are the averaged functions obtained from two female spider monkeys. Each data set has been best fit (continuous and broken lines) with linear summations of photopigment absorption functions having peak values appropriate for the two L/M pigments characteristic of spider monkeys, that is, with peak values of 550 nm and 562 nm (Jacobs & Deegan II, 2001). As can be seen, in each case this procedure provides an excellent account of the spectral sensitivity measurements. Note that in this example the relative proportions of the two pigments required for best fits are quite different for the two animals. For one monkey (triangles) the required L cone proportion was 80.4%, while for the other animal (circles) the best fit required much less of the L fundamental, 20.2%. The inference drawn from this is that these two trichromatic animals must have very different L:M cone ratios.

L:M cone ratios were derived for the 60 monkeys from spectral sensitivity functions of the sort illustrated in Fig. 1. The resulting distribution of L:M cone ratios is plotted in Fig. 2. Taken as a group, the monkeys of this sample were estimated to have nearly equal proportions of L and M cones, the average L cone representation being 49.6% (S.D. = 18.4%). For the most part the samples

Fig. 1. ERG flicker photometric spectral sensitivity functions of the sort used to estimate L:M cone ratios in platyrrhine monkeys. The results shown here were obtained from two spider monkeys (*Ateles fuscicollis*). As described in the text, their spectral sensitivity functions were best fit (continuous and broken lines) with summative combinations of M and L pigment spectra having $\lambda_{\max}$ values of 550 and 562 nm. The weights required for these fits are indicated.

Fig. 2. The distribution of L:M proportions in a group of 60 female platyrrhine monkeys. The relative representation of L and M cones was estimated for each animal using data of the sort illustrated in Fig. 1. The broken line was calculated from the binomial distribution as described in the text.

tation being 49.6% (S.D. = 18.4%). For the most part the samples from the several species represented are too small to yield any within-species inferences. However, for the two cases that did involve reasonable numbers of individuals (squirrel monkeys and spider monkeys) the species means for L cone representation were close to that obtained for the entire group of platyrrhines (45.1% (S.D. = 18%) and 55.1% (S.D. = 19%), respectively). The individual variation in L:M cone ratios appears to be distributed normally across this sample (Kolmogorov–Smirnov $D = 0.069$, $df = 60$, $P > 0.2$). A notable feature of this exercise is the indication of considerable individual variation in L:M cone representation. Significantly unbalanced ratios were relatively common in this sample with ~10% of the monkeys having an 80% or greater representation of one cone type.

Mechanisms influencing L:M cone ratios in platyrrhine monkeys

The results shown above appear to provide a reasonable indication of L:M cone ratios and their variations in heterozygous platyrrhine monkeys. The fact that the mean ratio for the sample of monkeys is very close to one is in accord with the idea (above) that random X-chromosome inactivation not only allows two cone classes to emerge in the retinas of heterozygous females, and thus allows trichromatic color vision, but that it is also likely a principal mechanism for the regulation of L:M cone ratios in platyrrhine monkeys.

In recent years X-chromosome inactivation has come under intensive study. It is a complex process controlled by a set of genetic elements that are located in a region of the X chromosome called the inactivation center (Migeon, 2002; Latham, 2005). Although some genes on the X chromosome escape inactivation (Carrel & Willard, 2005), a majority of all of the genes on either the maternal or paternal X chromosome are silenced. In mammalian somatic cells X-chromosome inactivation is generally considered to be a random process with regard to parental origin. However, it has become clear that a range of factors can influence choice and/or the maintenance of such choice with the result that the adult inactivation pattern may show bias toward one or the other of the X chromosomes (Migeon, 1998). In such cases, the

mosaic organization characteristic of heterozygous females shows an unbalanced representation of the two parental genes. For platyrrhine monkey cones this would presumably be reflected in unusual L:M ratios.

Three general processes have been identified as potentially important influences on relative gene representation in heterozygous females (Busque & Gilliland, 1998; Migeon, 1998). First, since only small numbers of cells are present at the time of X-chromosome inactivation, stochastic variations can by themselves lead to inequalities in the distributions of the two resulting cell populations. Second, randomness in the inactivation process can be distorted as a result of repressing or enhancing the activity of genes in the inactivation site (the XIST locus). Finally, following inactivation one or the other of the resulting cell populations may become disfavored for survival, for example, often because these cells contain a mutated gene that fosters a proliferative advantage or disadvantage. This latter process, cell selection, has been identified as a factor in a number of genetic diseases (Busque & Gilliland, 1998; Migeon, 1998).

The results shown in Fig. 2 provide both an indication of the average L:M ratio in this population of heterozygous female monkeys and an estimate of individual variation. Given that the L:M cone ratios in these platyrrhines are initially set by the process of X-chromosome inactivation, what might account for these individual variations? There is a large literature documenting deviations from 1:1 ratios between paternal and maternal X chromosomes in human females. When they are extreme such deviations have been referred to as "skewing," and they are often detected in females manifesting X-linked genetic diseases. The threshold for what constitutes skewing appears to be arbitrary, but is often defined as requiring expression of one allele in 75% or more of the cells (Busque & Gilliland, 1998), although values ranging between 70% and 90% have also sometimes been invoked, for example, (Racchi et al., 1998; Sharp et al., 2000; Sato et al., 2004). By those criteria a significant number of female platyrrhine monkeys would be judged to have skewed inactivation ratios. Of the potential mechanisms for producing variation in L:M cone ratios in these monkeys, cell selection would perhaps seem an unlikely candidate. Cell selection, typically said to be the most common cause of skewing (Migeon, 2002), is invoked when one or the other of the two genes favors or disfavors growth. Although the M/L opsin genes are in a real sense mutated versions of other opsin genes, they appear to function perfectly normally in that individual animals that express either or both of these genes have normal vision (Jacobs, 1984). Further, if it were operative, such cell selection would presumably consistently favor either L or M representation whereas, as illustrated in Fig. 2, extreme ratios in both directions appear nearly equally likely. It is thus not obvious how cell selection of this kind could be a factor that would bias the L:M cone ratios. These same arguments would also seem to make it unlikely that the ratios are being driven as a result of some distortion in the inactivation process. If both of these potential types of influence on ratio regulation seem unlikely to be at play, that would leave stochastic variation at the time of inactivation as the prime candidate for underlying individual variations in L:M cone ratios. If that is the mechanism, the size of the cell pool at the time of inactivation will be crucial. Unfortunately, neither the exact timing of X inactivation nor the numbers of cells that serve as precursors to cells in the neural retina are known for any species. If inactivation is indeed random, and if there is no subsequent bias imposed by development, then the binomial distribution can be used to estimate the number of cells present at the

time of inactivation from the relationship: cell pool size = $0.25 / \text{L:M ratio variance}$. Applied to the distribution of Fig. 2, such a calculation predicts that the observed degree of dispersion of individual L:M cone ratios would be achieved from a pool containing on average 7.4 cells at the time of inactivation (95% confidence interval: 4.0–8.9). The broken line in Fig. 2 was generated by calculating the variability resulting from a binomial function with this predicted pool size for a normal distribution ($n = 60$).

Functional implications of variations in platyrrhine monkey L:M cone ratios

These results show that although on average the M and L cones are about equally well represented in the retinas of trichromatic platyrrhine monkeys, there are some significant individual variations. For comparison, the range of L:M variation in these monkeys is equivalent to that seen in the retinas of human males with normal color vision (Carroll et al., 2002). These variations may hold implications for vision in platyrrhine monkeys and, perhaps, for understanding human vision as well.

L:M cone ratios have often been estimated using the techniques employed here, that is, fitting weighted sums of M and L cone fundamentals to measurements of spectral sensitivity. By definition then these variations in cone ratios manifest variations in spectral sensitivity. Accordingly, the L:M cone ratio variations documented for platyrrhine monkeys directly predict variations in the normal weighting of photic stimuli. Some of these variations may be large enough to be significant. For example, one of the trichromatic phenotypes characteristic of monkeys from the family Cebidae combines M and L cone pigments with peak values at about 536 nm and 562 nm (Jacobs & Deegan II, 2003). Two such animals having cone ratios drawn from the respective extremes of the distribution of Fig. 2 would be predicted to show threshold sensitivity differences amounting to about 0.4 log units for a 650-nm light. Whether such differences in visual capacity are significant under natural viewing conditions is not known, but it would not be surprising if they were.

The other potential impact of variations in L:M cone ratios is on the quality of color vision. That topic has been the subject of a number of studies done on human subjects with, however, sometimes contradictory outcomes. For instance, although several classical measures of color discrimination were found not to differ for a pair of individuals that had highly divergent L:M cone ratios (Miyahara et al., 1998), chromatic contrast sensitivity seems to depend on L:M cone ratio with sensitivity highest for subjects whose ratios were closest to unity (Gunther & Dobkins, 2002). Similarly, although the spectral location of unique yellow has been sometimes found to reflect L:M cone ratio variations (Cicerone, 1987; Gowdy & Cicerone, 1998; Otake & Cicerone, 2000) it has even more frequently been judged to be independent of such variations (e.g., Wesner et al., 1991; Mollon & Jordan, 1997; Brainard et al., 2000; Knau et al., 2002). Given this lack of clear agreement it is hard to know if the natural variations in L:M ratios seen among trichromatic platyrrhines do impact color vision in any significant way. We do note however that laboratory color vision tests done on humans usually feature optimized viewing conditions (e.g., long exposure times, highly saturated lights, spatially simple viewing arrangements) and it could be that any advantages or disadvantages of strongly unbalanced L:M ratios become more evident as viewing conditions become more challenging as they are in natural environments where, for example, variations in

illumination conditions, partially obscured targets, and limited viewing time are often the order of the day.

Finally, these results may hold some implications for understanding human color vision. Including both subtle changes in the X-chromosome opsin genes that result in only very small spectral shifts in the resultant photopigment and those gene alterations associated with classical color vision defects, many human females are heterozygous at the opsin gene sites (Deeb, 2005). In such individuals the relative representation of the two gene products will presumably be subject to the same influences as those determining L:M proportions in platyrrhine monkeys. There have been many studies of vision in carriers of color vision defects (Jorgenson et al., 1992; Jordan & Mollon, 1993; Miyahara et al., 1998; and the references therein). Among other things, these studies reveal a considerable degree of individual variation in the effects of the presence of an altered gene array with some women having effectively normal color vision while others show significant change. At least part of that seems likely to reflect the variations in gene representation resulting from X-chromosome inactivation. Assuming that process is common across primates, the statistics of the distribution of Fig. 2 may be used to infer how L:M cone ratios will be impacted by X-chromosome inactivation in individuals with different opsin gene arrays.

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