Human Potential for Tetrachromacy

by Kimberly A. Jameson

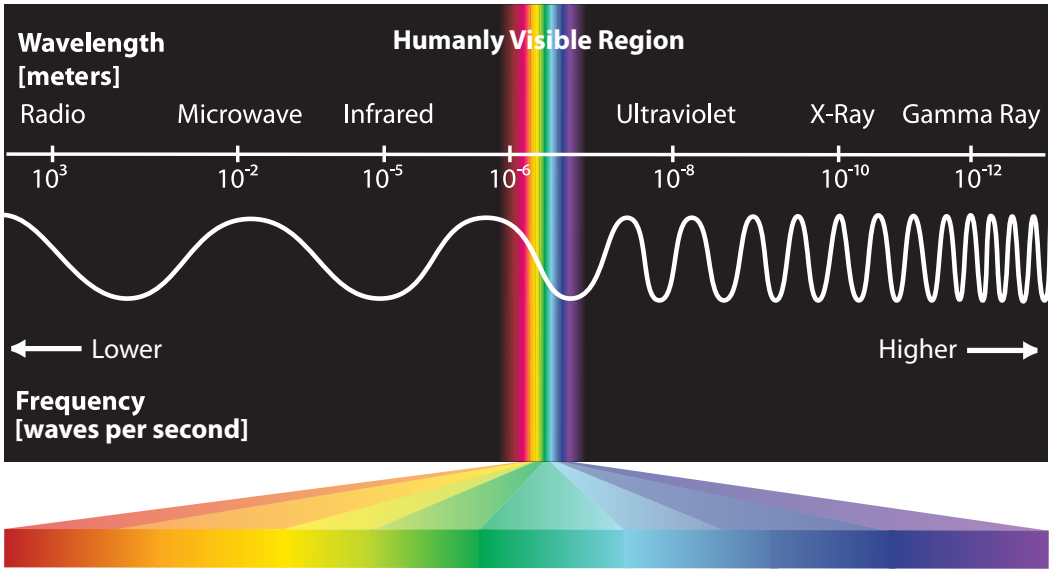

Figure 1. *The Sun's electromagnetic spectrum with the small portion that is visible to humans highlighted by pseudo-coloring. Scale shown is approximate, created based on information from The U.S. Department of Energy Lawrence Berkeley National Laboratory website (www.lbl.gov/MicroWorlds/ALSTool/EMSpec/EMSpec2.html).*

Nature's color palette—the changing sky, autumn leaves, the tinted irises of beloved eyes—has allured human interest since time immemorial. Scientific advances over the past twenty years have led to a far better understanding of the relevance and physiological basis of color experience than ever before. Recent research in molecular genetics, color perception and cognitive psychology is clarifying the underpinnings of human color sensations, how color experience has evolved, and along which perceptual paths we might be headed as a species of color-experiencing individuals. Together, such advances suggest that extensions of color perception theory are needed to account for retinal photopigment diversity unanticipated by accepted models of color vision trichromacy.

Why do we experience color?

The ability to perceive color is so natural that we rarely consider its origin. Color perception, like perception of texture or motion, occurs when our visual system encounters illuminated objects. This ability to detect surface variation by sampling the light, or spectra, reflected off environmental objects is widespread across species. Humans enjoy color by processing reflected spectra within a narrow (~380 nm to ~780 nm) "visible" range of electromagnetic wavelengths (Figure 1). Color requires both (i) photon capture by photoreceptors and (ii) encoding of photoreceptor excitation ratios.

The number of colors humans can distinguish varies across individuals, and is generally estimated to be between one and ten million. Perceived color variation is due to the ways our available photoreceptors react to reflected light. Photoreceptor response sensitivities also underlie *metameric* color equivalence classes (object reflectance spectra that have different physical forms but produce the same color percept) (Figure 2). The existence of natural and man-made metameric

classes of reflectance spectra, and their variation *vis-à-vis* observer's photopigments, give strong evidence that profiles of light reflected off objects are not uniquely colored. Indeed, object reflectance spectra are only electrical and magnetic pulses of photon energy waves, which do not *contain* any color, or even have any visual features. Thus, color is an internal construction.

What is color vision for?

Despite the non-unique mapping from color to reflected light, color cues are used in detecting targets against dappled backgrounds, perceptual segregation and object identification or categorization by color.[1] During non-human primate evolution, an ability to detect color differences from surface reflectances was likely selected for because it provided a means of signaling for the species. Perhaps color permitted the identification of carbohydrate rich fruit or tender leaves,[1, 2, 3, 4, 5] or aided social interaction through detecting physiological states of conspecifics.[6, 7, 8] The benefits of such color vision capabilities may have played an important role in the evolution of non-human primates into humans. Thus, although color is not a physical property of the world, and considerable color perception variation exists among humans, the ability to perceive color in the environment seems evolutionarily important.

The genetic basis of color vision.

As mentioned, color stems from object reflectance spectra, through comparisons of different photoreceptor class signals that arise from the probabilistic capture of reflected photons from a usable portion of the electromagnetic spectrum. The contrast encoding of receptor excitation is essential because a photoreceptor whose sensitivity distribution peaks around 540 nm only communicates the varying presence stimulating light to the brain, not its wavelength. It only says "I'm responding, I'm responding!" it does not communicate "I'm responding and I'm greenish!" The "greenish" part of the message comes when signals from different photoreceptor types are subsequently compared, beyond the retina.

Humans derive color information from responses of typically three cone classes containing different photopigments, distributed by the millions across the retina. These different cone classes are generated through expression of different opsin genes. Opsin genes with different amino acid sequences and a light-absorbing chromophore can produce photoreceptor classes with drastically different absorption spectra.

Genetic sequences identified for human light-sensitive pigments include: (a) the chromosome-3 linked rod rhodopsin pigment[9] that interacts with color vision at low

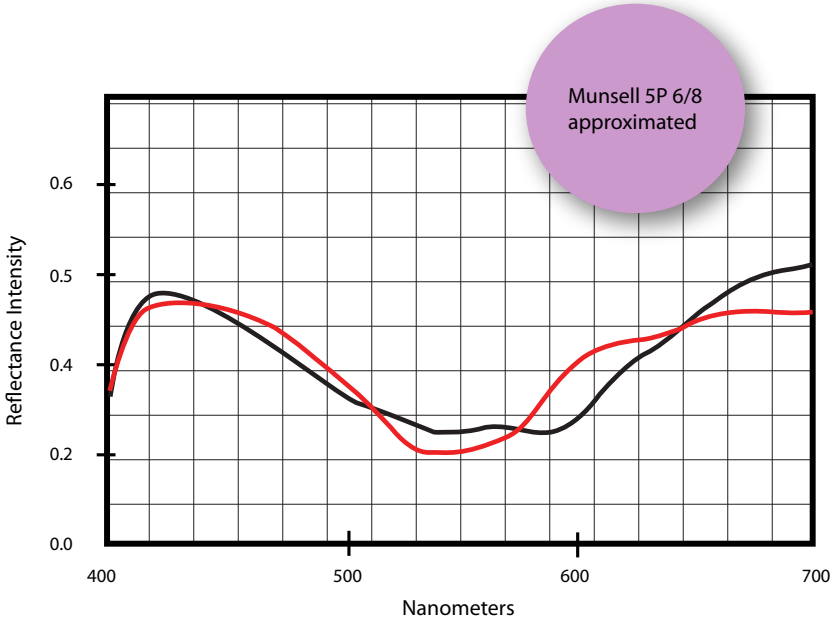

Figure 2. *Two curves showing metameric reflectance spectra under a standard observer model. Both reflectances produce the same lavender color appearance (Munsell color chip 5P 6/8) shown approximated by the inset circle. The lavender screen sample of Munsell 5P 6/8 was rendered Aug. 26, 2009 at www.myperfectcolor.com/Match-of-Munsell-5p-6-8-p/mpc0110461.htm. Special thanks to Professor A. Kimball Romney for providing the reflectance spectra for use here*

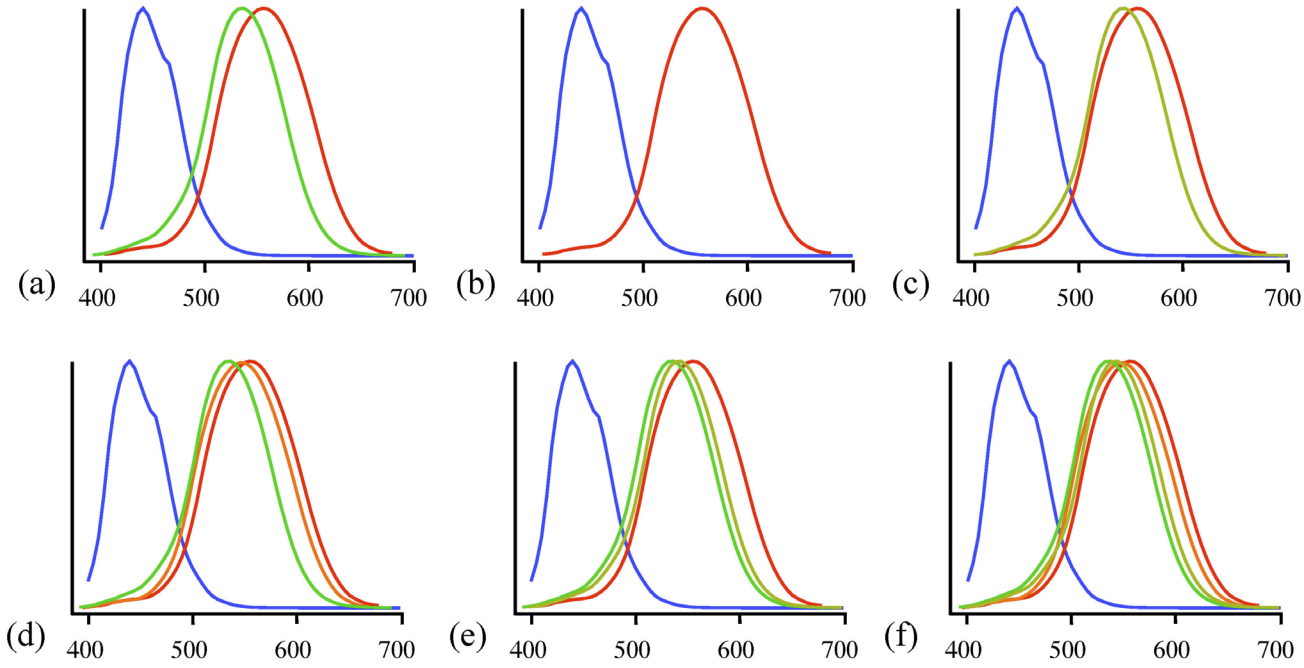

Figure 3 *(above). Several known and estimated variations in human retinal phenotypes linked to variation in photopigment opsin genes. Curves illustrate the responsivity of different photoreceptor classes to the electromagnetic spectrum.[46] Top row depicts known observer models, bottom row depicts estimated observer models. Panel (a) shows a normal trichromat observer with short- (SWS), medium- (MWS) and long- (LWS) wavelength sensitive photopigment classes; (b) a deficient dichromat, a form classically known as "Daltonism" (a Deuteranope-type missing MWS photopigment)[19]; (c) an anomalous trichromat (Deuteranomalous with shifted MWS photopigment); (d) a retinal tetrachromat with two LWS pigment classes in addition to the usual SWS and MWS photopigment classes; (e) a retinal tetrachromat with two MWS in addition to SWS and LWS photopigment classes; and (f) a retinal pentachromat with two MWS and two LWS photopigment classes in addition to the SWS photopigment. Uncertainty and debate exist regarding the phenotype expression of forms (e) and (f).*

light levels; (b) the chromosome-7 linked short-wave sensitive cone photopigment; and (c) the X-chromosome linked middle- and long-wave sensitive cone photopigments.[10] Genes for the X-chromosome linked photopigments are the basis for our color sensitivity at the mid- and long-wave portions of the visible spectrum, M-opsins and L-opsins, respectively, and share 98% gene sequence similarity.[11, 12, 13] The structure and function of X-linked opsin genes reveal much about their evolutionary purpose as a highly adaptive component of the visual system. Several genetic features support this idea. First, considering naturally occurring genetic variations, the ability to differentiate appearances of predominantly long-wavelength frequencies from medium-wavelength frequencies arose in our primate ancestors via straightforward X-linked *gene duplication* – a key process in evolving new gene functions. Second, a single missing or different amino acid (called "SNP" for single-nucleotide polymorphism) in certain portions of the opsin gene sequence produces dramatic shifts in the visual response to light.[14, 15] And third, duplication, divergence, intra- and inter-genic cross-overs and unequal recombination are all normal operating procedures for M- and L-cone opsin genes.

These opsin gene features contribute to differences in retinal photopigment response properties. Figure 3 shows typical retinal photopigment responses (a), compared to several variations (b-f).

The initial identification of opsin gene sequences yielded unexpected M- and L-opsin gene variation.[16] Subsequent research found many M- and L-opsin gene sequence variants are systematically linked to the peak responses of photopigment absorption curves.

Measuring spectral response properties of different photopigment variants *in vivo* is complicated by varying optical density of pigments, cell "wave-guiding" morphology, and ocular media filtering. Nevertheless, variations in color vision phenotypes are traceable to genetic variation, so it's viable to use individual opsin genotypes to investigate behaviors associated with phenotype variation.

Interestingly, the X-linked inheritance of these photopigments implies that some women have different long-wavelength sensitive opsin genes on each X-chromosome and, consequently, the genetic potential to express more than the usual three photopigment classes (see online supplement at www.

glimpsejournal.com/2.3-KAJ.html#1). These heterozygous females are among those considered *putative retinal tetrachromats*[17] and may express (in addition to rods) four retinal cone classes, each with a different spectral sensitivity distribution, thus having the potential to experience tetrachromatic vision.[18]

Individual variation and color perception experience.

Much human color perception research has explored the impact of individual differences in photopigments on color perception. Response curves of observer types in the top row of Figure 3 are well-understood. Figure 3 shows (a) a normal Trichromat; (b) a deficient Dichromat; and (c) an Anomalous Trichromat. Types (b) and (c) are measurable color perception deficiencies.

Figure 3 (d), (e) and (f) show less well-understood forms of normal individual variation that approximate phenotypes which in theory could arise due to expressed opsin gene variation. Demonstrating such types *in vivo* is difficult due to considerable response similarity among the photoreceptor classes. However, their existence has been described in several studies.[17, 18, 20, 21, 22] Existence of type (d) individuals with four distinct retinal cone classes is now generally acknowledged, even if types (e) and (f) are still debated.[13] Type (d) is key here, and is referred to as a retinal tetrachromat.[22, 23]

Figure 3's message is that flexibility in the structure of the X-linked opsin genes facilitates change in the genetic basis for human color vision. This same flexibility is widespread across species[12] perhaps suggesting that evolving opsin gene variety itself poses no inherent evolutionary disadvantages.

What do individual differences imply for emergent tetrachromacy?

The observer modeled in Figure 3(d) is a retinal tetrachromat, and possibly a *functional tetrachromat*[23] who might experience color perception differences compared to a normal trichromat, and could exhibit non-normative color processing behavior on certain color perception tasks[18] (see online supplement at www.glimpsejournal.com/2.3-KAJ.html#2). Figure 4 simulates some color perception differences arising from variations shown in Figure 3(a-c) and illustrates that under such observer variations object color is clearly observer-dependent and cannot *belong* to the object.

Understanding these normal individual differences and color vision deficiencies[24] help us appreciate: (1) the extent of natural variation in color perception, (2) how little such differences have mattered historically with respect to color utility, and (3) the implications for emerging tetrachromacy at both observer- and species-level.

Figure 4. *Illustration approximating the appearance of a United States Flag for color vision normals and some color deficient observers. Courtesy of the National Archives (University of Wisconsin, Americana collection, 1437652)*

Neitz et al. suggested that "extra pigment types in people with normal color vision are sufficiently different to support tetra- or even pentachromacy," but like most early researchers, downplayed the possible effects of retinal tetrachromacy, further stating, "The fact that they don't indicates that the trichromacy of normal vision has its origin at a level of the visual pathway beyond that of the cone pigments, likely beyond the receptors."[25]

Recent results demonstrating perceptual consequences of retinal tetrachromacy complicates this accepted model of trichromacy. A three-channel post-receptor processing constraint would eviscerate new information available through retinal tetrachromacy by reducing it to a trivariant signal. Observing that signals from additional photoreceptors get used, and yield variation in perceptual experience, therefore requires an update to accepted theory. This remains a topic of considerable debate.

Is the idea of potential human tetrachromacy really so strange?

Since the discovery of allelic variants of human long-wavelength and medium-wavelength photopigments, there's been a good deal of popular speculation about the implications for color perception. For example, the *Financial Times*, "Weird Science" section explored "Women Who Can See More Than Red" (March 10, 2001, p. 11).

The potential for human tetrachromatic color perception need not be spun into a Sci-Fi fantasy of beings with supranormal vision. In fact, opsin gene diversity within primate species, and the natural adaptive flexibility of opsin gene structure and function, both foreshadow a real potential for human tetrachromacy in the evolutionary pipeline.

Already, evidence of tetrachromacy exists in a number of animal species (see online supplement at www.glimpsejournal.com/2.3-KAJ.html#3). While most mammals are dichromats, three to five photopigments are otherwise common. At the upper extreme are mantis shrimp which seem to make use of eleven different photopigments.[26] Responding, in part, to environmental changes, formerly trichromatic fish species have evolved several extra photopigments in as short as 1-2 million years, and this is linked to species' opsin gene diversity driven by evolutionary selection pressures[27] (see online supplement at www.glimpsejournal.com/2.3-KAJ.html#3a). Opsin gene diversity and flexibility is also seen in non-human primates. Some New World primates exhibit considerable opsin gene diversity within species[28] (see online supplement at www.glimpsejournal.com/2.3-KAJ.html#3b). Old World primate studies comparing human and chimpanzee opsin genes suggest an ongoing processes of gene conversion for some human photopigment opsin genes[29, 30] (see online supplement at www.glimpsejournal.com/2.3-KAJ.html#3c). And advances using transgenic therapy have transformed dichromat primate individuals into trichromats, permitting otherwise unexperiencable color sensations, and demonstrating that rapid, dramatic changes are possible in the primate neural coding of color[31, 32] (see online supplement at www.glimpsejournal.com/2.3-KAJ.html#3d).

But isn't human trichromacy already optimized for our environment?

Shepard describes human trichromacy as the most effective way to visually process and encode terrestrial light.[33] However, considering that many other terrestrial animals need more than three functional photopigment classes, the optimality of the human system feels anthropocentric. Additional complications come from species with more than three photopigments operating in spectral ranges not hugely different from humans. The European Starling's color discrimination performance, for example, suggests that at least some of the bird's three photopigments couple with a fourth (that peaks in the near UV) within the range of 400-700 nm (see online supplement at www.glimpsejournal.com/2.3-KAJ.html#3e). Thus, in the human visible range, Starling tetrachromacy is a viable form of color processing.[34]

What are the selection pressures that might cause tetrachromacy to emerge?

The possibility of human tetrachromacy raises two intriguing considerations: (1) what visual processing demands provide positive selection pressure for tetrachromacy? and (2) what would color vision be like for a tetrachromat?

We don't know the answers to either question, but recent investigations of putative female tetrachromats are places to start. Research has found color perception differences (albeit, subtle) in comparisons of possible tetrachromat women with trichromat controls.

Rigorous psychophysical studies of potential tetrachromat color perception exist,[20, 21, 35] but are equivocal on the precise variation experienced under retinal tetrachromacy. Limitations in display technology and stimulus presentation formats may have historically hindered demonstration of such differences, if they exist, using traditional psychophysical methods.[23] Investigations attempting to avoid such obstacles employ increased stimulus complexity and more

naturalistic color processing conditions and behaviors.[17, 22, 36] These investigations used molecular genetic methods to identify potential retinal tetrachromats and found differences in perceptual behaviors when the genetic potential for more than three photopigment classes was present. Behaviors differentiating tetrachromat genotypes from trichromat controls included: (1) perceiving more colors in diffracted spectra;[22] (2) correlation between performance variation on a standardized test for trichromacy and indices of richer color experience;[17] and (3) color similarity and color naming pattern variation found in shared group consensus measures from potential tetrachromats compared to female trichromat controls.[36]

These results show that when color judgments were made in empirical conditions that approximated more naturalistic viewing circumstances (e.g. binocular viewing of contextualized large-field stimuli), processing variation correlated with human tetrachromacy was easier to demonstrate. But more specifically, the results show that the genetic potential to express more than three cone classes correlated with differences in color categorization, naming and color similarity judgments.

Such results imply real world consequences for individuals with extra opsin genes. For example, Jameson et al.[17] suggests that one color vision test widely used in industry and the military can inadvertently classify putative tetrachromats as deficient when they may actually have richer color perception experience.

Moreover, Sayim et al.[36] found that in some portions of color space individuals with tetrachromat genotypes shared, as a group, cognitive color-similarity representations and a color linguistic code with higher consensus (compared to trichromat controls), perhaps reflecting color expertise among such individuals. Such findings may suggest why individuals vary greatly regarding color judgments in art, publishing, architecture and design.

Finally, concerning color categorization research, one might think the existence of specialized groups of color observers in a population would create problems for a population's evolution of a shared color naming and categorization system. That is, if subsets of a society's individuals use different perceptual categories for identifying objects, how can successful communication occur among all members, and how could a shared color communication system evolve?

We used computer simulation approaches from evolutionary game theory to investigate such questions using simulated color category learning scenarios.[37, 38, 39, 40] Our results showed no obstacles to evolving stable categorization solutions in populations that include agents modeled with normal, deficient and putative tetrachromat discrimination data. Indeed, some aspects of population observer diversity actually help color categorization systems form and stabilize in simulation scenarios.[37, 38] If analogous to color category evolution in real world linguistic societies, these results suggest that no significant communication obstacles would be expected from societies comprised of realistic proportions of normal, dichromat and tetrachromat individuals, each with varying forms of color perception and potentially different salient color categories for object identification and communication.

Speculations on a future for tetrachromacy...

The foregoing gives clues concerning how human tetrachromacy might prove advantageous today, but we can't predict which kinds of present-day color judgments herald behavioral advantage for the long-term. It's possible that early non-human primate mutations in the gene structure may have been largely due to selection pressure from the environment, whereas more recent mutations may be additionally driven by social and sexual forms of evolutionary pressure. Under changing circumstances, several future evolutionary scenarios are plausible:

Interpretation of human emotion states.

Changizi et al.[41] suggested trichromacy evolved to detect important physiological states using color correlates of blood-oxygenation levels among non-human primates. So too, color correlates of emotion states might be important cues for successful social interaction and appropriate interpretation of emotion expressions among human conspecifics.[42]

Disease detection.

Historically, color perception has been important in medicine. Medical practitioners note red in a rash, yellowness of jaundice and the colors of a healthy body.[43] Modern day doctors use color stains in cell histology and color codes on medical instruments.[24] Color deficient doctors may miss symptoms because of an inability to perceive the color of disease.

Informally we observed results that, although unpublished, are consistent with the idea that tetrachromacy may inform us about the uses of color in evolving technologies, for example, in medical diag-

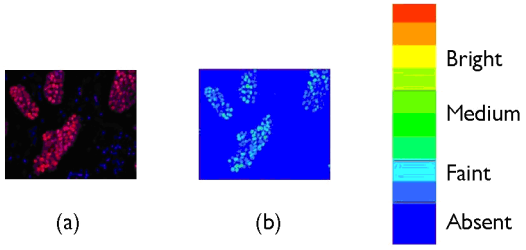

Figure 5. *Digitized image (b) at right translates the fluorescent intensity of each cell in image (a) at left using the chromatographic scale shown at right. The scale shows that the brighter the cell, the more protein expressed. Raters count the number of bright, medium and faintly stained cells. The potential problem is that detection of the medium cells is likely to be different for raters possessing opsin gene polymorphisms (i.e., putative tetrachromats) compared to those who do not.*

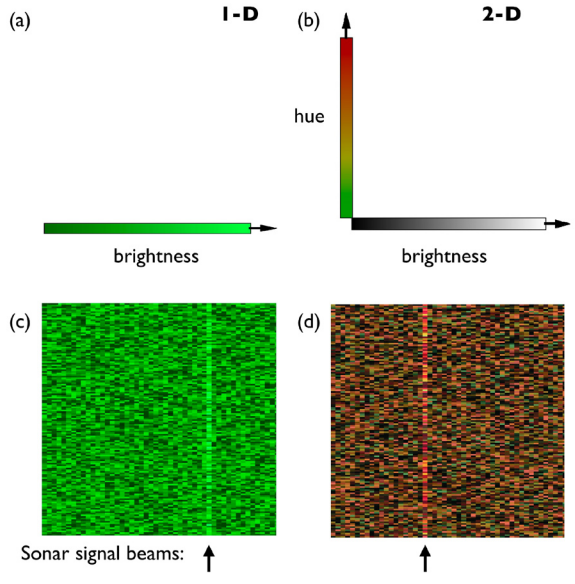

Figure 6. *Multidimensional information coding: panel (a) shows the one dimensional gradient code used in monochrome (green) brightness code. Panel (b) shows two dimensions of a combined brightness and color code. Panel (c)--showing a sonar signal beam in monochrome code--and Panel (d)--showing a signal in a brightness-color code--show the two forms of the displays tested in visual processing circumstances experienced by sonar scope operators in U.S. military applications and college undergraduates.[44]*

nosis. We found that laboratory assistants with tetrachromat genotypes gave different pathology diagnoses when certain cell stain scales were used in histology studies. Figure 5 (b) shows an example of the type of fluorescent cell marker (with adjacent color scale), that when used to color code panel (a) produced different estimates of cancer cell detection by potential tetrachromats compared to observers without such potential.

Co-evolutionary social pressures along these lines may have served in the past, and could serve in the future, as factors encouraging human tetrachromacy.

Processing color in contextually rich information displays.

Using color to identify objects involves combining different types of information, or perceptual dimensions, during information processing. While trichromacy gives greater color discrimination, studies show that color deficient dichromats may be better at detecting targets in color camouflage.[44] Dichromats do this by picking out targets using luminance differences that get drowned out for trichromats by the chromatic content they appreciate. Such signal processing is a consideration for modern information displays, because while display designers want to simultaneously present all sorts of information, not all observers can easily interpret multidimensional display codes. Jameson and colleagues examined whether a one-dimensional brightness code typically used in sonar applications (Figure 6(a)) could be combined with a second dimension of color code (Figure 6(b)) to add an extra layer of information to the standard data display.[45] They found that normal trichromat observers could extract two forms of information from the 2-dimensional display codes on par with the 1-dimensional code performance. Thus, observers (i) reliably detected slightly brighter signal beams in the multicolored panels (Figure 6(d)), while (ii) correctly identifying information conveyed by color in the same display (e.g., whether a signal was primarily reddish, greenish, or yellowish). Dichromats would find task (i) easy, whereas task (ii) would be difficult for a dichromat with red-green confusion.

This ability to extract two forms of information from a combined code exemplifies how color dimensions could be easily separated under human tetrachromacy.

It's unclear whether in contextually-rich scenes tetrachromacy might permit identification of signal dimensions overlooked by trichromats when displayed information encodes two, three or

four dimensions of data. Obviously any such tetrachromat performance difference may be both subtle and might apply for some portions of the color space but not others.

Summary

The story of photopigment evolution suggests human tetrachromacy may be in the pipeline. Visual pigments of vertebrates evolved about 500 million years ago (mya). Precursors of modern day human visual pigments were likely an adaptation that began in the Cretaceous period, around 150 to 80 mya. The flexibility of the opsin gene structure has permitted adaptive changes in the past, and is almost certainly ready to adapt if needed in the future. There's no need to assume that an evolutionary zenith is realized in modern human photopigment opsin genes. If the human species survives long enough, some selective advantage, or form of co-evolution, may provide strong a justification human color vision tetrachromacy. There seem to be distinctly different ways to think about emergent human tetra-chromacy:

On the one hand, one can entertain the possibility that human tetrachromacy reflects an on-going, natural, evolutionary potential for human visual processing. If a need arose in our environment (like dramatic environmental changes seen during the Cretaceous period, or a highly valued social trend that established a uniform color bias) human photopigment genes would be ready to meet the challenge.

On the other hand, a narrower approach focuses on sensationalizing deviations in perceptual experience brought about by tetrachromacy compared to trichromacy (cf. the *Financial Times* "super-perceiver" perspective noted earlier).

Of these, the view of human tetrachromacy as a natural evolutionary potential seems more useful. Considerable color perception variations already exist among and within dichromat, anomalous trichromat and normal trichromat observer groups without major behavioral consequences or evolutionary meltdowns. Further research should show human tetrachromacy to be correlated with subtle individual color perception variations that are no more problematic than those that already exist. While the impact of potential human tetrachromacy may turn out to be important for some applications, in general, its impact is likely to be nonproblematic at the practical levels of modern life. Even so, tetrachromacy is highly significant for theories of perception and theories of human evolution.

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Color (vol 2.3)

Human Potential for Tetrachromacy (supplement to print article)

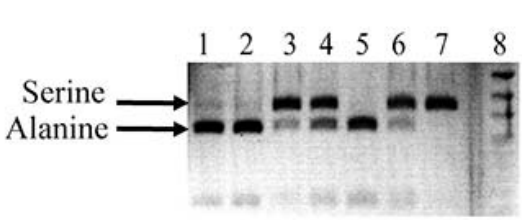
by Kimberly A. Jameson, University of California, Irvine

[**NOTE:** This web site is optimized for Firefox, IE, Safari and Chrome browsers. If you encounter display issues, please try a supported browser.]

Section 1: Identifying human individuals with the genetic potential for tetrachromacy.

The genes encoding the opsins or apoproteins of the human "red" and "green" photopigments are each composed of six exons and are arranged in a head-to-tail tandem array located on the q-arm of the X-chromosome.[1,2,3,4] Individuals with normal color vision usually have one red opsin gene in the proximal position of the gene array and one or more green opsin genes. These X-linked opsin genes have 98% identity in nucleotide sequence (including introns and 3' flanking regions).[5] The genes encoding long- and medium-wavelength apoproteins differ by an estimated fifteen residues, seven of these known to occur at positions which influence photoreceptor responsivity in the expressed phenotype.[6,1,7] Amino acid sequence differences across M- and L-cone genes are at codons 116, 180, 230, 233, 277, 285 and 309. Of these, seven single nucleotide substitutions (SNPs) at three particular sites (codons 180, 277 and 285, exon 3) produce substantial shifts in photopigment spectral sensitivity,[8] and sensitivity shifts increase monotonically with substitutions.[7,9]

Molecular genetic methods used by Jameson and colleagues were developed between 1997 and 2002 and are described in Wasserman, Szeszel and Jameson.[10] Existing studies,[7,11,12,13,14] which together distinguish the genomic regions of DNA sequence variation between MWS and LWS genes, provided the empirical justification for the Wasserman et al.[10] method used in the human tetrachromacy research discussed here by Jameson and colleagues. The Wasserman, Szeszel & Jameson (2009) procedure uses a combination of three molecular approaches in order first to create MWS and LWS gene-specific DNA templates and then to use those templates to distinguish between their respective codon 180 sequences. A long-range polymerase chain reaction technique generates gene-specific PCR products. A PCR and a restriction digest determines MWS and LWS codon 180 genotypes (Figure 1), and DNA sequencing of each PCR template confirms this gene specificity (Figure 2). The method extends the analyses of Jameson et al. (2001) by permitting greater specificity of the identified polymorphisms and permits a more informative analysis of genotype-correlated behaviors reported by Jameson et al.[15]



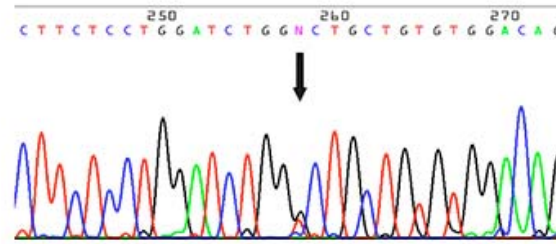


Figure 1. *Identifying the presence of protein substitutions on opsin genes illustrated by DNA radiogram (left panel) and DNA sequence trace (right panel). Fnu4HI restriction digestion assay of genomic DNA from exon 3 codon-180 of the M-cone opsin photopigment gene of seven female donors (Lanes 1-7). DNA radiogram (at left) shows the presence of the DNA sequence coding for Alanine is detected as a 160 bp band whereas the DNA sequence coding for Serine is detected as a 190 bp band. Lanes 1, 2 and 5, genomic DNA from human females with alanine at exon 3, codon-180 of the green gene. Lane 7, one female with serine at exon 3, codon. Lanes 3, 4 and 6, females with a serine-alanine dimorphism at exon 3, codon-180 of the green gene. Dimorphisms were confirmed by sequencing (graph at right) where the arrow indicates equal strength signals at a specific locus. Lane 8, DNA Ladder. Restriction gel digest products depicting analogous dimorphisms occurring at codon-180, exon 3 of the red opsin (L-cone) gene are not depicted here, but are similar to that shown for the green gene. Images courtesy of the author.*

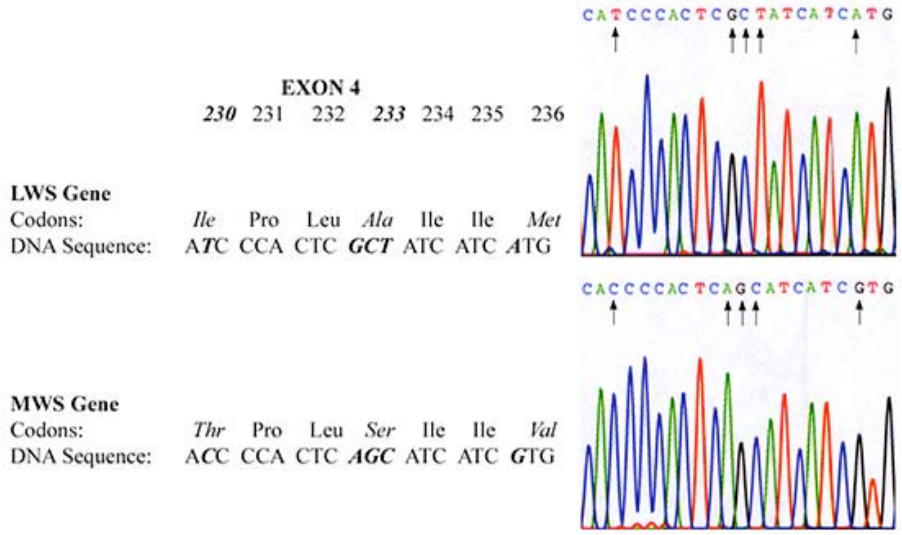


Figure 2. *Distinguishing M- from L-opsin genes. Opsin genes for M-cone photopigments were distinguished from those for L-cone photopigments using a long range polymerase chain reaction (PCR) technique. The method provided gene-specific sequences within exon 4 of the red (LWS) and green (MWS) opsin genes. DNA sequence coding was used to confirm specificity of each long-range PCR product. Amino acids and DNA bases unique to each gene are shown in bold and italics. Images courtesy of the author.*

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Section 2: Perceptual differences associated with retinal tetrachromat genotypes.

Some human females have different M- and L-opsin genes on each X-chromosome and, as a result, the genetic potential to express more than the usual three retinal photopigment classes. These heterozygous females are *putative retinal tetrachromats* and may express (in addition to rods) four retinal cone classes, each with a different spectral sensitivity distribution, and the potential to experience tetrachromatic vision.[16] Frequency estimates of females who are potential tetrachromats range between 15% and 50%,[17] whereas less is known about the true frequency of expressing four retinal cone classes.

Although four-channel visual processing is known to occur when human trichromats simultaneously use rods and all cone classes under mesopic viewing conditions (when light conditions are low but not dark), and the expression of four retinal cone classes is accepted, still functional photopic human color tetrachromacy is debated. Color processing theory limits humans to no more than a trivariant color signal. Thus, four retinal cone classes may be a necessary (but not a sufficient) condition for full tetrachromatic color perception, since, for full tetrachromacy, four channels of cortical color signal processing also seem to be needed.[18]

Research has explicitly sought to demonstrate what perceptual differences (if any) are experienced by human retinal tetrachromats compared to trichromat controls with the usual 3-photopigment retinas.[15, 16, 19, 20, 21] Still, there remains uncertainty among color vision researchers regarding whether individuals with diverse photopigment opsin genotypes should be viewed as individuals with color perception variations from normal.

What has been shown is that candidate retinal tetrachromats exhibit non-normative performance on some standardized psychophysical color vision assessment measures. As discussed by Cohn, Emmerich and Carlson[22] heterozygous females fail to be detected by the use of an anomaloscope, although there are reported shifts in their anomaloscope color matches[23, 24, 25, 26, 27] as well as shifts using flicker photometry.[24, 28] Heterozygous females were also found to exhibit higher absolute thresholds to small spots of red light.[26, 29] Unlike normal controls, these heterozygotes exhibit a failure of additivity of trichromatic color matches after exposure to a light bleaching of the rod system.[19] However, some results, such as those described by Birch,[30] indicate that female compound mixed heterozygotes for protan and deutan color deficiency are usually reported to have normal, not deficient, color vision.

Compared to the earlier work in the area, Jameson and colleagues,[15, 31,21] took a slightly different approach and aimed to demonstrate perceptual differences associated with retinal tetrachromat genotypes under more realistic viewing circumstances and stimulus formats than those typically employed. One assessment method they examined[21] was the Farnsworth-Munsell 100-hue test (FM100).[32]

The FM100 is a color vision assessment test widely used in industry and the military for screening color deficient or anomalous individuals from jobs that may critically depend on color judgments. The FM100 stimulus is a series of color samples that form a continuous hue circle, discretized into 85 color “caps” forming a smooth gradient of hue, ostensibly at a fixed level of brightness and a fixed level of saturation.

The outer color perimeter of Figure 3 approximates the 85-cap hue gradient. The test is administered to individuals as a set of randomized colors from a quadrant of the hue circle, one quadrant at a time. The observer’s task is to re-order the randomized colors until they form a perceptually smooth hue series, or to “correctly order” the color continuum so no visible transpositions in hue occur. *If* an individual performs with zero errors on this sorting task, *then* the color “caps” should be ordered without transposition errors and the transposition line traced in the polar coordinate plot of Figure 3 would resemble a smooth continuous line near the central region of graph. This is clearly not the case for the transposition line traced by the data shown in Figure 3. That is, in Figure 3 the large jagged excursions away from the inner concentric circle of the graph indicate that this heterozygote observer performed as poorly as a color deficient subject might on this sorting task. The individual’s *Total Error Score* equals 132, indicating a diagnosis of *low color discrimination*, which would in all likelihood exclude this individual from many delicate color processing scenarios in industry and the military. However, in every other respect this individual exhibited no sign of color perception deficiency, and reported no sense of diminished color experience or color confusion.

In general, this seemingly contradictory finding was seen in several of the putative tetrachromats assessed by Jameson et al.[21] That is, several individuals with tetrachromat genotypes performed very poorly on the FM100 diagnostic, but generally experienced no color vision impairment or weakness and exhibited increased sensitivity for detecting chromatic bands in a diffracted spectrum task.[15] Interpreting these results, Jameson and colleagues[15,21] suggest that the color perception of some female carriers of protan deficiencies can differ from that of female trichromat controls but not in a deficient way. Rather, in some color discrimination tasks protan carriers may be unimpaired, (detecting chromatic contrast at levels resembling those of trichromat controls [33]), while under other viewing circumstances or tasks (e.g., in a chromatic banding task) they may detect more categorical color differences compared to trichromat controls.[15]

An alternative explanation of the poor FM100 performance of some of these putative tetrachromats was offered by Jameson et al.[21] That is, based on the actual performance data they suggest that such tetrachromats required a personal “correct” ordering that does not exactly follow the FM100 stimulus sequence. In this scenario, a putative tetrachromat may exhibit transpositions in the sorting task that disagree with the diagnostic’s standard sequence. This personal ordering scenario is possible if in some

cases FM100 cap transpositions reflect an unimpaired individual's non-normative just-noticeable-difference (jnd) variation along one or more color space dimensions (rather than sorting errors due to poor color sensitivity). This is an interesting alternative interpretation of abnormal performance on a standardized test of color perception, which raises prospects for further demonstrating differences in retinal tetrachromat color processing.

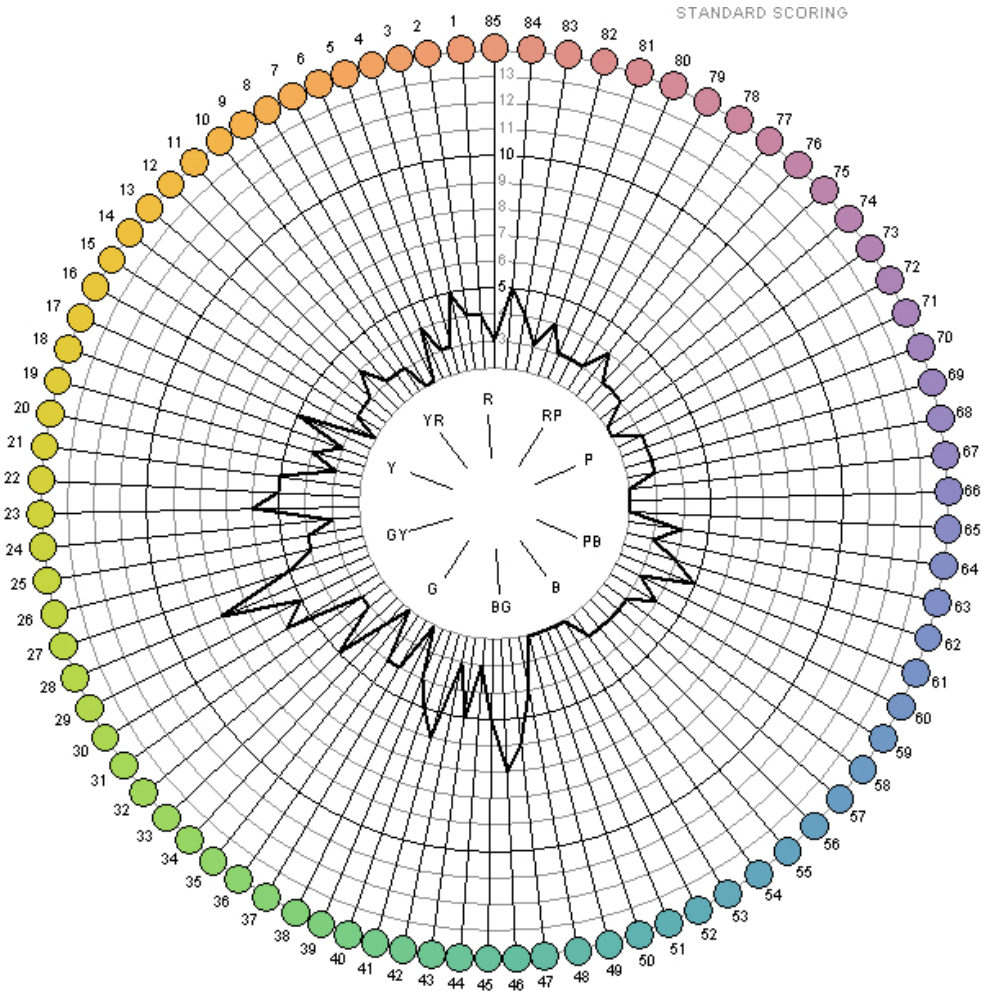

Figure 3. *Polar coordinate plot of performance on the Farnsworth-Munsell 100-hue test (FM100) for a female individual with a diverse photopigment opsin genotype (reported as Subject 85 in Table 1 Jameson, Bimler & Wasserman, 2006).*[21] *Genotype determined using the Wasserman et al.*[10] *method found this individual heterozygous for both X-chromosome linked opsin genes--or a female heterozygote with a codon-180 dimorphism for the L-cone opsin (L-opsin Ser-180-Ala), and a codon-180 dimorphism for the M- cone opsin (M-opsin Ala-180-Ser). Despite otherwise excellent color perception, FM-100 compression parameter analyses showed that this individual's patterns of FM100 confusion were displaced in a direction corresponding to a 15° axis in a polar coordinate compression parameter space.*[21] *The FM100 performance shown indicates this individual performed very poorly compared to normative age-adjusted performance by an average Z value equal to 2.54 standard deviations and is likely diagnosed as false-positive deficient. This subject otherwise had unimpaired color perception, zero errors on the Ishihara pseudo-isochromatic plates, and reliably perceived 12 different chromatic bands in the Jameson et al.*[15] *diffracted spectrum task, which is significantly greater than the average chromatic banding observed for trichromat female controls. Copyright Kimberly A. Jameson. Image courtesy of the author.*

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Section 3: Implications for potential human tetrachromacy from other species.

Subsection 3a. African Cichlid fish illustrate adaptive flexibility in opsin gene structure and function.

Species interacting with environmental changes and other selection pressures can undergo the flexible evolution of photopigments in as short as 1-2 million years. For example, the hundreds of species of colorful cichlid fishes derived from the same ancestors in the Great Lakes of Africa evolved seven unique cone opsin genes, producing visual pigments sensitive to wavelengths from the ultraviolet to the red end of the spectrum.[34] Cichlid visual pigment variation (Figure 4) is driven by both natural selection (e.g., a range of evolved foraging behaviors) and sexual selection (strong selection for conspicuous male color patterns). Species differing in the sets of opsin genes expressed also have differing visual sensitivities. Some cichlid species express three visual pigments to produce a trichromatic visual system, while others express four visual pigments (e.g., species from Lake Malawi). Which sets of genes are expressed in part depends on positive selection in species adapted to changing habitats, such as environments with varying turbidity or lake depths. Slight changes in cichlid pigment gene sequences cause visual pigment shifts that can alter mating preferences and other cichlid behaviors.[34] Thus, in theory, the expression of more than three distinct classes of photopigments is directly linked to a species' opsin gene diversity, which is driven by evolutionary selection pressures.

Figure 4. *Hundreds of colorful Cichlid fish species evolved in the Great Lakes of Africa and are known for their ecological diversity. Cichlids illustrate the plasticity of opsin gene structure and function since, in addition to illustrating the roles of strong positive selection, they can finely tune visual pigments by changing the complement of expressed opsin genes. Such differential gene expression tunes and produces differences in visual pigment sensitivities between species with nearly identical opsin gene sequences.[34] Image by flickr member: Trebz.*

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Subsection 3b. Some New World primate species also exhibit opsin gene flexibility.

Opsin gene diversity and flexibility is also seen in non-human primates. Generally, Old World primates (sub-Saharan Africa and Asia) tend to be trichromatic and New World primates (Central and South American) dichromatic. Research shows that some New World monkeys--the Squirrel Monkey, Spider Monkey, Marmoset and Dusky Titi--are color vision polymorphic species in which the base condition is dichromacy, but a considerable proportion of individuals are trichromats. In some cases, such as the Dusky Titi (*Callicebus Moloch*, Figure 5) considerable opsin gene diversity is know to exist within species.[35]

Figure 5. *Dusky Titi (Callicebus Moloch) diurnal primates who as a species are polymorphous for color vision. Callicebus is unusual compared to other New World primates, in which three available types of M/L photopigments are typical: the species has a total of five M/L cone photopigments types available for expression. Their special social structure could be interacting with their atypically diverse opsin genotypes through coevolution: Males & females forage for food in groups, and males share in caretaking of offspring, grooming and in caring for the infants with females. Image by flickr member: cliff1066*

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Subsection 3c. Opsin gene evolution in Old World Primates and humans.

Continued opsin gene evolution in humans is also supported by comparisons between humans and Old World primates. Using molecular population genetics approach to compare human and chimpanzee opsin gene variation, patterns of long-wavelength gene variation in humans were found consistent with positive selection, or gene conversion; whereas the patterns of LWS variation in chimpanzees were characteristic of purifying selection variations.[36] These results suggest an ongoing process of gene conversion for some human photopigment opsin genes, and further work will provide a more complete understanding of its dynamics and what specific opsin gene features the homogenizing conversion is acting on.[37]

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Subsection 3d. Curing "color blindness" in the Squirrel Monkey.

Of great interest is the recent transgenic research conducted by Katie Mancuso, Jay Neitz, Maureen Neitz and colleagues.[38, 39] These researchers demonstrated that within a few months of being treated with an L-opsin-coding gene therapy, adult squirrel monkeys (*Saimiri sciureus,* Figure 6) exhibit changed spectral sensitivity and richer color perception behaviors, and are effectively transformed from dichromat to trichromat individuals. This shows the surprising result that even in mature primates post-receptoral neural plasticity exists, and rapid, dramatic changes are possible in the neural coding of color when these animals were provided the genes to express an extra photopigment.

Figure 6. *The squirrel monkey (Saimiri sciureus) species possesses opsin genes that are ideal for attempting a transgenic cure for dichromacy.[39] In the squirrel monkey gene pool are three variants (or "alleles") of the X-linked cone photopigment gene: one coding for a protein similar to the human M-photopigment (with pigment absorption maxima around 538 nm), a second coding for a protein similar to the human L-pigment (with absorption maxima around 561 nm), and a third coding for a pigment with light-absorption properties roughly midway between the first two (around 551 nm). By having two X-chromosomes, a female squirrel monkey might inherit two different longer-wavelength alleles (one on each of her X-chromosomes), and in this way she'll acquire trichromacy (for more on these genetic mechanisms see Jacobs and Nathans 2009).[40] However, about a third of all female squirrel monkeys, will inherit the same pigment allele on both their X chromosomes and end up as dichromats, like the dichromat male squirrel monkeys. It is the latter female genotypes that were additionally missing the L-cone opsin gene that Mancuso and colleagues performed their transgenic cure for dichromacy.[39] Image by flickr member: mape_s.*

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Subsection 3e. Other terrestrial species have evolved color vision tetrachromacy in the spectral region "visible" to humans.

It is easy to think that human trichromacy in its current state is already optimized for our environment. After all, if it wasn't optimized we'd notice, right? To understand the implications of this idea on human color procesing it helps to consider other terrestrial animals that require more than three functional photopigment classes that operate in approximately the same spectral window that humans use. That is, species that have color processing systems with operating ranges that are not hugely different from those of humans, but which have more degrees of variation than a trichromatic system. One example is the European Starling (the small to medium-sized passerine bird, Figure 7). In addition to a visual pigment that peaks in the near UV (at 362 nm), Starlings have three photopigments that roughly resemble the long-, medium- and short-wave sensitive pigments of humans. Although the European Starling UV pigment peaks outside the lower limit for the human operating range (i.e., shorter than 400 nm), one tail of the UV pigment responds considerably, and overlaps with all of the other Starling photopigment response curves, within a 400 nm to 700 nm range (Figure 8). Color discrimination performance suggests that at least some of the Starling's other pigment curves appear to be coupling signals with the UV pigment.[41] Thus, the case of the European Starling suggests that within a humanly usable range of ~400 nm to ~700 nm, tetrachromacy is clearly a viable form of color processing for these birds.

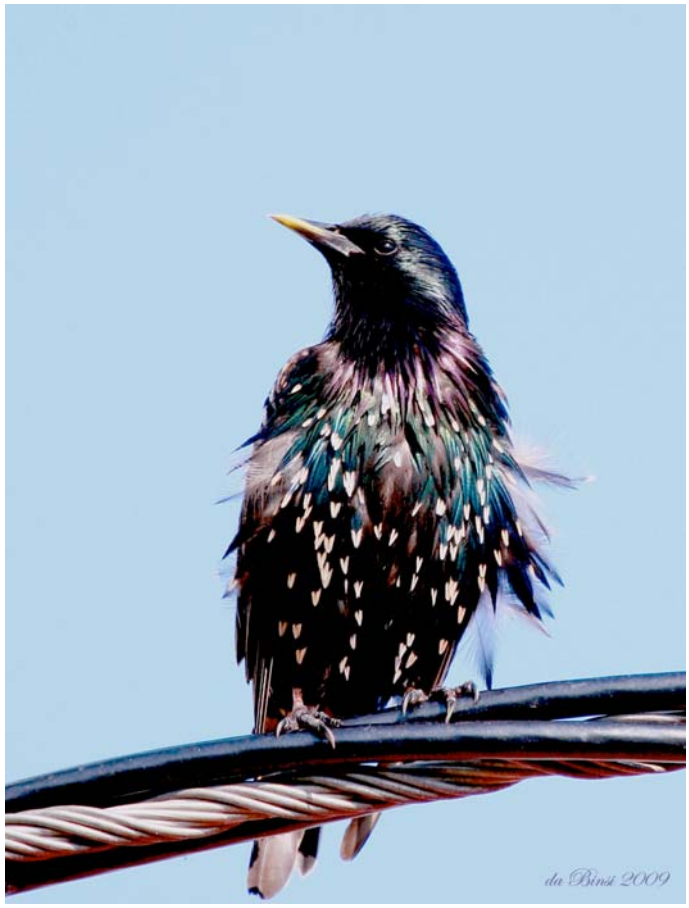

Figure 7. *The European Starling (Sturnus vulgaris), a common bird native to most of temperate Europe and western Asia, is a color vision tetrachromat. Image by flickr member: daBins.*

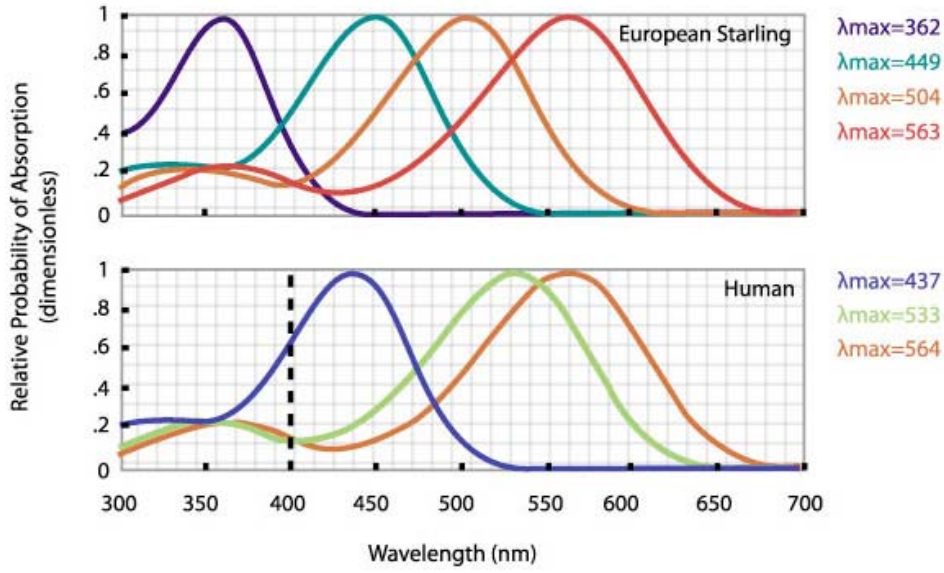

Figure 8. *European Starling sensitivity (top) compared to human photopigment sensitivity (bottom). The important point to note is that although the Starling's UV pigment peaks outside the lower limit for the human operating range (i.e., shorter than 400 nm), one tail of the UV pigment responds considerably, and overlaps with all of the other Starling photopiment response curves, within the "humanly visible" ~400 nm to ~700 nm range. The substantial overlap among sensitivity curves, in addition to the birds' color discrimination*

performance, suggests that at least some of the Starling's other pigment curves appear to be coupling signals with the UV pigment. Together these features suggest an achieved increase in discrimination that is of significant enough chromatic resolution to justify an evolutionary adaptation. Image adapted from Palaeontologia Electronica (http://palaeo-electronica.org/2000_1/retinal/fig_7.htm).

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