The locus of color sensation: Cortical color loss and the chromatic visual evoked potential

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Color losses of central origin (cerebral achromatopsia and dyschromatopsia) can result from cortical damage and are most commonly associated with stroke. Such cases have the potential to provide useful information regarding the loci of the generation of the percept of color. One available tool to examine this issue is the chromatic visual evoked potential (cVEP). The cVEP has been used successfully to objectively quantify losses in color vision capacity in both congenital and acquired deficiencies of retinal origin but has not yet been applied to cases of color losses of cortical origin. In addition, it is not known with certainty which cortical sites are responsible for the generation of the cVEP waveform components. Here we report psychophysical and electrophysiological examination of a patient with color deficits resulting from a bilateral cerebral infarct in the ventral occipitotemporal region. Although this patient demonstrated pronounced color losses of a general nature, the waveform of the cVEP remains unaffected. Contrast response functions of the cVEP are also normal for this patient. The results suggest that the percept of color arises after the origin of the cVEP and that normal activity in those areas that give rise to the characteristic negative wave of the cVEP are not sufficient to provide for the normal sensation of color.

Introduction

Color vision can be disrupted or lost by a number of causes, the most common being genetic mutations. Achromatopsia is a condition wherein the percept of colors is absent. Much more common is dyschromatopsia wherein there is a partial loss of color capacity. Many cases of achromatopsia and most cases of dyschromatopsia are inherited as mutations of the photopigment genes expressed in the cone photoreceptors (recently reviewed by Neitz & Neitz, 2011) and consequently are retinal in origin. In addition, many cases of acquired color vision deficits also have a retinal origin. Acquired deficiencies predominantly diminish function in the short-wavelength cone pathway and consequently affect blue-yellow color vision capacities (e.g., Verriest, 1963; Adams, 1982). Cerebral achromatopsia is a condition wherein color capacities are lost due to damage at the cortical level (e.g., Meadows, 1974; Cowey & Heywood, 1997). In most cases, the color loss is incomplete and thus is more appropriately considered a form of dyschromatopsia. Cerebral achromatopsia and dyschromatopsia are most commonly associated with an infarct in the occipitotemporal region of the cortex (Jaeger, Krastel, & Braun, 1988; Bouvier & Engel, 2006). The condition rarely occurs in isolation with patients often exhibiting constellations of symp-

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toms, including visual agnosia, visual field losses (hemi- and quadrantanopias), and sometimes memory deficits, depending upon the extent of the lesion.

The visual evoked potential (VEP) is a recording of the brain activity in response to visual stimuli. VEP recordings have been shown to correlate with both threshold and suprathreshold psychophysics (e.g., Campbell, Kulikowski, & Levinson, 1966; Campbell & Maffei, 1970, Campbell & Kulikowski, 1972; Regan, 1989; Kulikowski, 1991). The VEP has been used clinically for many years to assess visual losses in myriad conditions involving both cortical and subcortical origin (e.g., traumatic brain injury, multiple sclerosis, optic nerve damage, and retinal diseases). About 40 years ago, investigators showed that reversing patterns of isoluminant colors could produce strong responses generated by chromatic pathways (e.g., Regan, 1973; Regan & Spekreijse, 1974). Nonetheless, most clinical VEPs utilize reversing black and white checkerboard stimuli, which are not designed to assess color vision losses. However, many color vision deficits can be measured and classified electrophysiologically by using a more refined version of the chromatic technique known as the chromatic onset visual evoked potential (cVEP) (e.g., Murray, Parry, Carden, & Kulikowski, 1987; Berninger, Arden, Hogg, & Frumkes, 1989; Kulikowski, Murray, & Parry, 1989, Rabin, Switkes, Crognale, Schneck, & Adams, 1994). The cVEP has been shown to be a sensitive and reliable measure of color losses in both congenital and acquired color vision deficiencies of retinal origin (e.g., Crognale, Rabin, Switkes, & Adams, 1993; Crognale, Switkes, et al., 1993; Buttner et al., 1996; Schneck, Fortune, Crognale, Switkes, & Adams, 1996; Schneck et al., 1997). Color vision deficits of retinal origin are easily revealed by differences in the waveform of the cVEP. Response waveforms of individuals with color vision deficits have lower amplitudes and increased latencies in the dominant negative- going component when stimuli designed to reveal their particular class of deficiency are used (e.g., Crognale, Switkes, et al., 1993).

To date, there have been few reports of the effects of achromatopsia of cerebral origin on the waveform of the pattern onset cVEP. Setälä and Vesti (1994) and Adachi-Usami, Tsukamoto, and Shimada (1995) each reported on a patient with dyschromatopsia who showed normal black and white as well as color pattern reversal responses, leading them to conclude that early luminance and color areas were intact. The way in which cerebral stroke would be expected to affect the cVEP would depend on the origin of the cVEP response components relative to the site of cerebrovascular insult. Unfortunately, the source of the characteristic negative component of the cVEP is not known with certainty. Previous work has suggested that the cVEP must originate fairly early in the cortical pathways because it is robust to modulation by attentional mechanisms (Highsmith & Crognale, 2010). Prior fMRI and PET investigations suggest that specialized cortical processing of color information occurs in early retinotopic regions within the ventral, occipitotemporal cortex (e.g., Lueck et al., 1989, Engel, Zhang, & Wandell, 1997; McKeefry & Zeki, 1997; Hadjikhani, Liu, Dale, Cavanagh, & Tootell, 1998; Wandell, Baseler, Poirson, Boynton, & Engel, 2000; Wade, Augath, Logothetis, & Wandell, 2008; Cavina-Pratesi, Kentridge, Haywood, & Milner, 2010). However, it is not clear whether or not fMRI and cVEP responses share physiological substrata. It is also not known at what level of cortical processing the sensation of color arises, that is, whether the color percept arises at a later stage in visual processing or if it is simply the cumulative product of the pattern of activity at each stage in the cortical stream.

Given the paucity of information regarding the source of the cVEP and the physiological substrate for the perception of color experience, it is difficult to predict the effects that achromatopsia might have on the cVEP. One possibility is that the sensation of color arises as the sum of activity in all of the color cortical circuits and that normal function at all levels as well as feedback circuits are requisite for normal color experience. In this case, one would expect abnormal cVEPs to be evident in the case of cerebral achromatopsia. Alternatively, if color experience arises at a late stage as a result of feed forward processing and if the source of the cVEP is at an earlier stage, then cerebral achromatopsia with sparing of earlier regions may not result in a diminished cVEP.

To investigate this series of questions, we tested a neuropsychological patient with acquired cerebral dyschromatopsia. This otherwise healthy patient experiences color deficits following an ischemic event damaging occipital and temporal cortical regions. We report both behavioral and electrophysiological measurements of color capacity. To preview our findings, the results reveal severe losses in color perception of a general nature paired with no disruption of the cVEP. Because the deficits are revealed in typical tests of low-level color vision (e.g., discrimination) and are not limited to color naming, they cannot be construed as resulting from a more general agnosia. Taken together, these results suggest that the percept of color arises after the origin of the cVEP and that normal activity in those areas that give rise to the characteristic negative wave of the cVEP are not sufficient to provide for the normal sensation of color.

Patient history

MC1 is a 45-year-old female former math teacher with a master's degree in math education. A vertebral

artery stroke in 2005 caused bilateral ventral occipito-temporal damage. The presumed cause of her infarct was intense coughing that tore her vertebral artery and subsequently produced an embolus. Acute MRI scans revealed the ultimate restoration of normal blood flow. MC1 currently has normal health, and she currently works editing mathematics textbooks and tutoring students. Her remaining vision is corrected to normal.

Acute diffusion scans provide limited visualization of the initial lesion location and volume. These initial scans reveal asymmetrical lesions in ventral occipito-temporal regions extending anteriorly and bilaterally to the posterior aspect of the parahippocampal gyrus. In the right hemisphere, the lesion extended medially into the precuneus at the level of the parieto-occipital fissure. In the left hemisphere, the lesion terminates inferior to the right hemisphere lesion. Because these initial scans were of limited quality, we report below results from recent high-resolution anatomical scans.

Patient MC1 has preserved vision exclusively in the right inferior quadrant accompanied by macular sparing. She states that she must deliberately remember to look up because she forgets about her visual field deficits. Her primary visual symptoms include achromatopsia, prosopagnosia, and topographical agnosia. When she describes her visual experience, she reports that the world appears in "sepia tones" and that colors are desaturated. She self-reports prosopagnosia and relies on voice to recognize people. More formally, in a recognition test of famous faces, MC1 provided incorrect names of the wrong gender and race even though she later reported knowing who each of the famous people were. She also describes her topographical agnosia as "having great difficulty navigating." For example, three blocks from her home of five years, she reported not knowing if she was close to her house until she could read the street signs. In our laboratory, she required guidance to and from the bathroom, located three doors away from the laboratory along a straight corridor. Furthermore, when tested on pictures of famous places, she named several outdoor places as indoor places and vice versa. MC1 has excellent verbal and written language production and comprehension as evidenced by conversation and written correspondence. She performs normally when tested on verbal comprehension and tests of auditory attention (see Table 1). Yet she describes word-finding difficulties when naming objects. Overall, MC1's affect is exceptionally cheerful and eager to participate. Finally, throughout testing, she places greater emphasis on accuracy rather than speed and frequently thinks aloud as she performs a task, providing some insight to her strategy. This is borne out by her slowed general processing time on the Wechsler Adult Intelligence Scale (see Table 1).

We presented MC1 with a series of common visual illusions to establish whether her visual perception was generally normal. She was able to accurately describe images with slant, linear perspective, depth, occlusion, shadow, and the local/global features in Navon letters and the face/vase illusion. In summary, MC1 is able and willing to follow directions during testing. Her deficits become apparent when she is asked to name visually presented material.

Methods

Magnetic resonance imaging (MRI)

The acute MRI scan images collected at the time of stroke were difficult to read due to edema and due to questions regarding the chronic status of her lesion. We collected high-resolution, anatomical MRI scans in a GE Signa HDx 3.0 T scanner at Reno Diagnostics Imaging Center. T1-weighted anatomical data were acquired using a high-resolution 3-D spoiled gradient recovery sequence (SPGR; 248 sagittal slices, TE = 2.82 ms, TR = 6.27 ms, flip angle = 8°, 1 × 1 × 1 mm^3 isotropic voxels with .5 mm spacing).

Behavioral color tests

A battery of standard color vision tests was administered to completely characterize the extent of MC1's color losses. These tests included the Ishihara test (38 plate edition), FM 100, D-15, Desat D-15, Rayleigh and Moreland matches (using an Oculus anomaloscope), Neitz Screening Test, Dvorine Plate Test, Farnsworth Lantern Test, and the Cambridge Colour Test. All plate tests and arrangement tests were conducted under a broad-spectrum lamp (Verilux) producing an illuminance of 920 lux with a color temperature of 5570 K.

Visual evoked potentials (VEPs)

VEPs were recorded to the onset (100 ms on/400 ms off) of sinusoidal chromatic gratings (1 cpd) of varying contrast that subtended 27° × 35° of visual angle. The space-averaged luminance of the screen was 16 cd/m^2. Stimuli were equated for individual isoluminance using a minimum motion paradigm (Anstis & Cavanagh, 1983) and stimulus colors were chosen to fall along the cardinal directions in MacLeod-Boynton, Derrington-Krauskopf-Lennie (MBDKL) color space. Modulations along the S axis preferentially modulate the S cones while holding the L and M cone activations

Test	Performance
Famous faces	*7/42 = 16.7%,* controls = 76.4%
Landmarks	*12/42 = 28.6%,* controls = 73.1%
WAIS	
Verbal comprehension	79th percentile
Processing speed	*23rd percentile*
Mini-mental status exam	28/30
TEA	
Elevator counting	7/7
Elevator counting, distraction	10/10
Lottery	9/10

Table 1. Summary of testing for famous faces and places. *Notes*: MC1's performance was compared to that of four age-matched control participants. Abbreviations: WAIS = Wechsler Adult Intelligence Scale, fourth edition; TEA = Test of Everyday Attention. *Italicized values indicate significantly abnormal (below normal) performance*.

constant. Modulations along the L-M axis preferentially modulate the L and M cones in opposition while holding the S cone activations constant. Such stimuli are believed to preferentially modulate the red-green and blue-yellow color opponent pathways. All colors were modulated around a white point (CIE x 0.31; y 0.32). The CIE coordinates of the endpoints at the maximum contrast employed along the cardinal axes were 0.28, 0.25 (S+); 0.36, 0.435 (S–); 0.36, 0.29 (L+/M–); 0.254, 0.349 (L–/M+). This resulted in nominal cone contrasts along the S axis of S = 59% and along the L-M axis of L = 6% and M = 11%.

VEPs were recorded using Grass gold cup electrodes, placed at Oz and referenced to Pz. A ground electrode was placed on the forehead. Electrode impedance was kept below 5 kΩ measured at 30 Hz. The signals were amplified (×50,000) and filtered (high-pass = 0.3 Hz; low pass = 100 Hz) using an isolated Grass bio amplifier, digitized at 1 KHz (National Instruments A/D board), and stored on a PC for off-line analysis. Recording, amplifying, and filtering procedures conformed to those recommended by ISCEV standards (Odom et al., 2010).

VEP responses were averaged over two randomly presented blocks of 64 presentations at each of five contrast levels. Contrast response functions were constructed for amplitudes and latencies of the first major negative component, which is believed to reflect the response of the chromatic pathways (e.g., Rabin et al., 1994). Contrast response functions were also measured from a group of color normal participants of varying ages ($n = 8$; average age = 23) and a separate group of participants who were close in age to MC1 ($n = 4$; average age = 47) because the chromatic VEP has been shown to change with age (Page & Crognale, 2005). Written informed consent was obtained from all subjects in accordance with the policies of the University of Nevada's Office of Human Subjects protection, and all procedures conformed to the Declaration of Helsinki.

Results

Magnetic resonance imaging

Figure 1 shows the extent of the lesion in our participant. Individual slices are sequenced from superior to inferior (from upper left to lower right section). The radiologist's report confirmed the location of encephalomalacic changes in the territory of the posterior cerebral artery. Specifically, the lesion is located bilaterally in the posterior parahippocampal, fusiform, and lingual gyri. The hippocampus is intact. In the right hemisphere, the lesion extended to the calcarine sulcus and the posterior cingulate gyrus, see Figure 1. The tissue damage is isolated to the posterior brain with the remaining brain tissue considered normal and no evidence of abnormal brain pressure. Furthermore, the lesion and symptoms remain stable.

Color vision tests

Ishihara test (38 plate edition)

MC1 tested as color deficient on the Ishihara Plate test. She missed plates 7, 9, 10, and 11. She was also slow and unsure on plates 13 and 17, taking more than the allotted 3 s. Observers with normal color vision typically miss few, if any, plates and respond quickly.

FM 100

On the FM 100, MC1 showed a generalized color loss (low discrimination) with a total error score of 600. Vingrys analysis (Vingrys & King-Smith, 1988) revealed a general color loss: angle = 71.83, C index = 4.92, S index = 1.31. A C index (measure of error severity) > 1.77 is considered abnormal; the S index (the selectivity or "scatter" measure) value indicates a nonselective loss (see Figure 2). Selective losses are typically > 1.97.

D-15

The D-15 revealed color discrimination problems with eight major crossings largely along a tritan axis with a total error score (TES) of 29.4. Normal TES is typically below 12. Any crossing is considered abnormal. Vingry's analysis revealed the angle = −87.5, C index = 3.10, and S index = 4.15 and indicated a

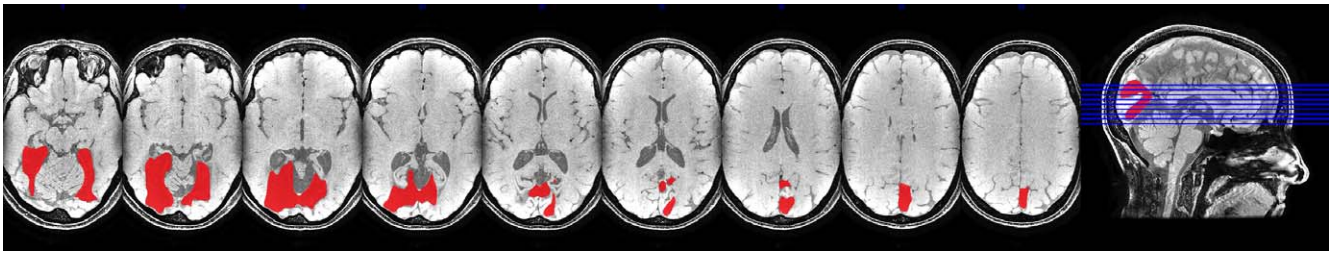

Figure 1. Axial anatomical MRI sections showing the extent of lesions in MC1. Anterior is shown as up. A large darkened region of scar tissue is evident in posterior and lateral regions.

significant color deficiency with selectivity along the tritan axis.

Lanthony's desaturated 15-hue test

MC1 produced six major crossings of a diffuse nature and included tritan and tetartan-like errors on Lanthony's desat 15 test. The total error score was 16.8 (Vingry's analysis: angle = 77, C index = 2.84, S index = 1.76). Normal index values for Vingry's analysis are given above.

Anomaloscope

On the Rayleigh match, MC1 made normal equations with an absolute matching range of 0.89–0.86 (anomalous quotients). On the Moreland match, MC1's range was from 0.8–0.7, also within normal for this anomaloscope. MC1 produced matches with normal midpoints consistent with her lack of a visual pigment-based color anomaly.

Neitz screening test

MC1 missed three of the six red-green plates but did not miss either of the two tritan plates. Missing any of these screening test plates is considered a reason for further testing.

Dvorine pseudo-isochromatic plates

MC1 missed plates 5, 9, 12, and 15 of the Dvorine test.

Farnsworth lantern test

MC1 failed the Farnsworth lantern test with four errors on the first run and a total of five errors on the second and third runs. More than two errors on the second and third test runs is considered abnormal.

Cambridge Colour Test (CCT)

The trivector portion of the CCT showed a normal (below 100) discrimination vector length for the protan axis (48) but abnormally large vector lengths for deutan (105) and especially tritan (227) discriminations. Three full discrimination ellipses (see Figure 3, left) demonstrated abnormally low discrimination with enlarged ellipses and axis ratios of 4.13, 2.11, and 2.54. Normal ellipse ratios are typically below 2. The orientations of the axes suggest a tritan deficit although discrimination deficits in other directions are also evident. Discrimination ellipses for a 54-year-old male observer with normal color vision are also shown (Figure 3, right) for comparison.

To summarize, MC1 has abnormal color perception as measured by all of these color measures except for color matching (anomaloscope). The color-matching results provided evidence for the presence of normal retinal pigments.

Visual evoked potentials

Sample waveforms for subject MC1 are shown in Figure 4. The shaded region indicates the average for the age-matched group ± 1 *SD*. The major components of the waveforms from MC1 are indistinguishable from the range of those observed in participants with normal color vision. Both the L-M and the S axis waveforms for MC1 have typical characteristics, including the prominent negative component that is believed to be the hallmark of the chromatic response (e.g., Murray et al., 1987; Berninger et al., 1989; Kulikowski et al., 1989; Rabin et al., 1994). The waveform components also have similar amplitudes and latencies as those from waveforms of color-normal subjects. Notably, MC1's waveforms lack a positive peak around 100 ms, a component believed to indicate luminance intrusion (e.g., Murray et al., 1987; Berninger et al., 1989; Kulikowski et al., 1989; Rabin et al., 1994). This latter result suggests that nominal isoluminance values were sufficient to isolate chromatic mechanisms for MC1.

It is interesting that MC1's waveforms appear to depart from the normal as a lack of prominence in the later components, particularly for the S axis. Whether or not this departure reflects actual differences in processing is uncertain because this is a single subject.

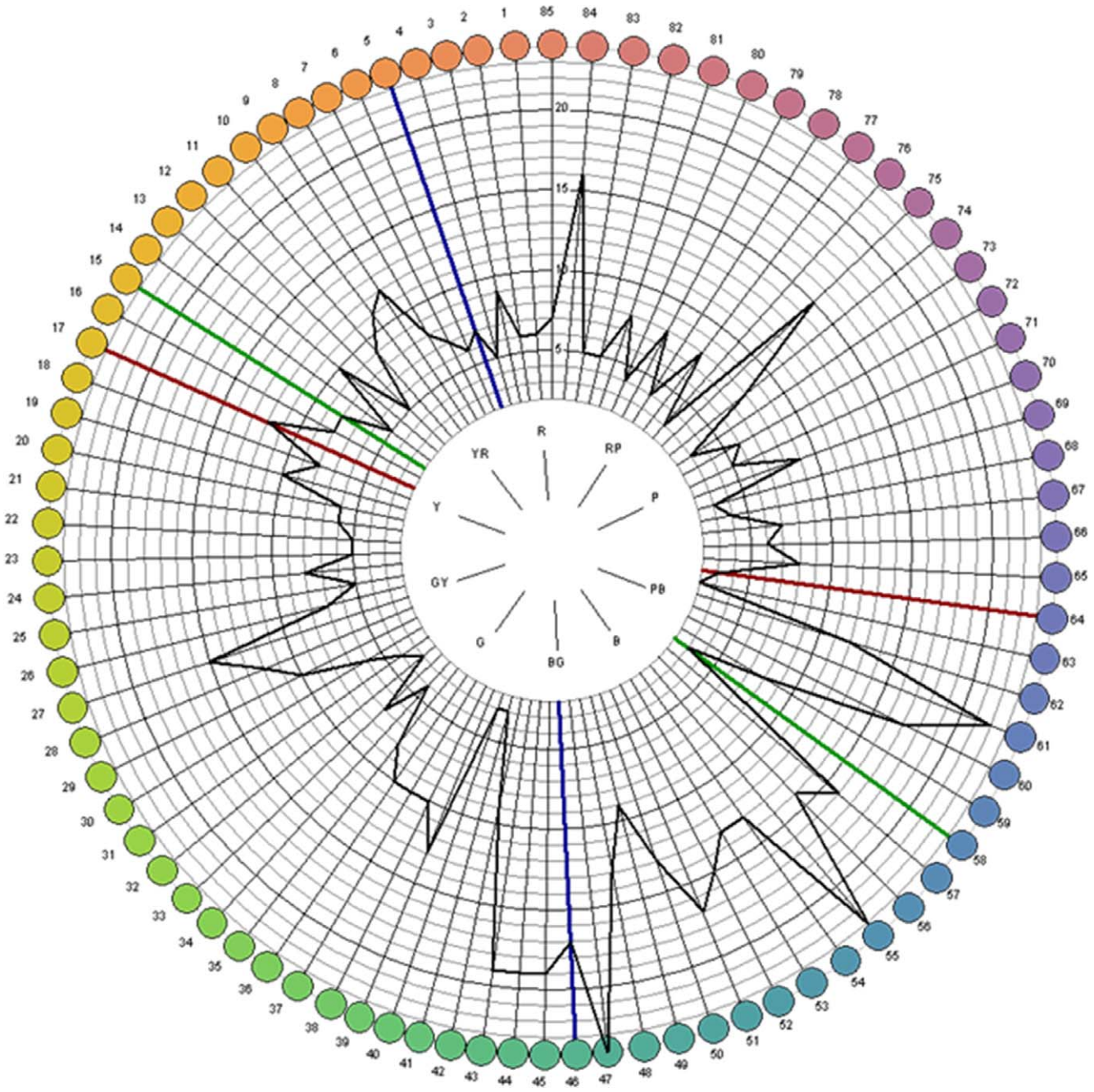

Figure 2. FM-100 error plot for subject MC1 showing large, generalized color vision losses. A perfect score corresponds to performance along the innermost ring. Greater distance from this central ring indicates increased severity of error. A number of small errors is considered normal. Tritan (blue), deutan (green), and protan (red) axes are indicated. Approximate colors of the caps are also shown.

However, should these waveform differences reflect actual differences in processing, then it is possible that they are indicative of deficiencies in later stages of processing or a loss of feedback from later stages.

Figure 5 (top panels) shows contrast-response amplitude functions obtained from participant MC1 in response to stimuli modulated along the S (left) and L-M (right) color opponent axes. The abscissa plots the percent of the maximum of the available monitor contrast on a log scale. The ordinate plots the amplitude of the response as measured from the largest negative deflection between 60 ms and 250 ms to the following positive peak. Also shown is the range of responses in our young and age-matched control participants. MC1 shows normal response functions that increase in amplitude along with increased contrast. Although response amplitudes are reduced in individuals with inherited or acquired color vision

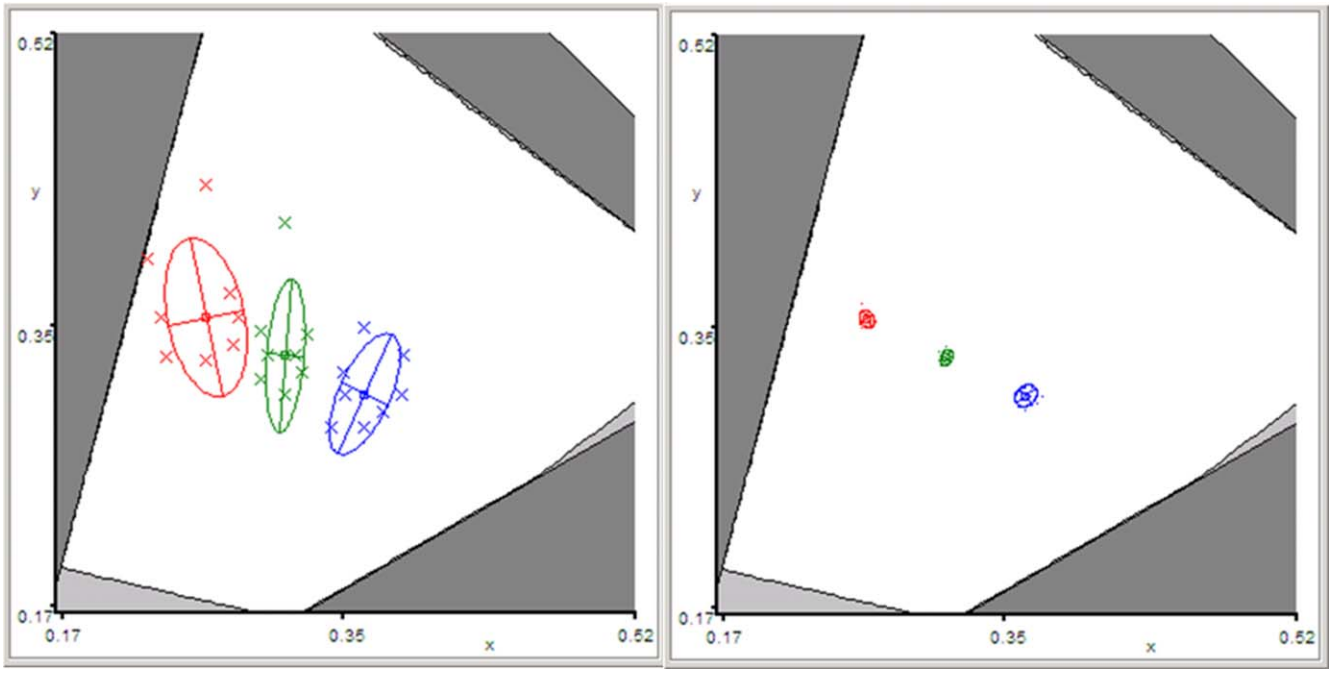

Figure 3. Discrimination ellipses derived from the Cambridge Colour Test plotted in CIE 1931 space for observer MC1 (left) and for a representative observer with normal color vision (right). The brighter white area within the gray regions indicates the region of attainable colors within the luminance limits of the stimulus monitor.

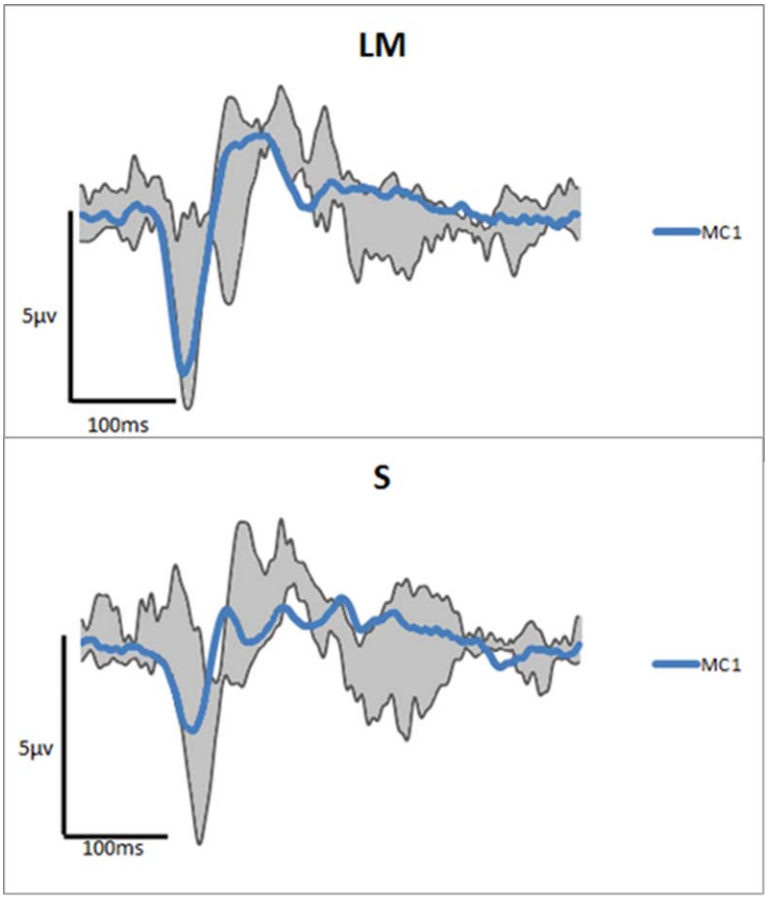

Figure 4. Example waveforms obtained from cerebral dyschromatopsia subject MC1 using stimuli modulated along the S and L-M opponent axes at high contrasts. The shaded regions indicate ± 1 *SD* around the average of the age-matched controls.

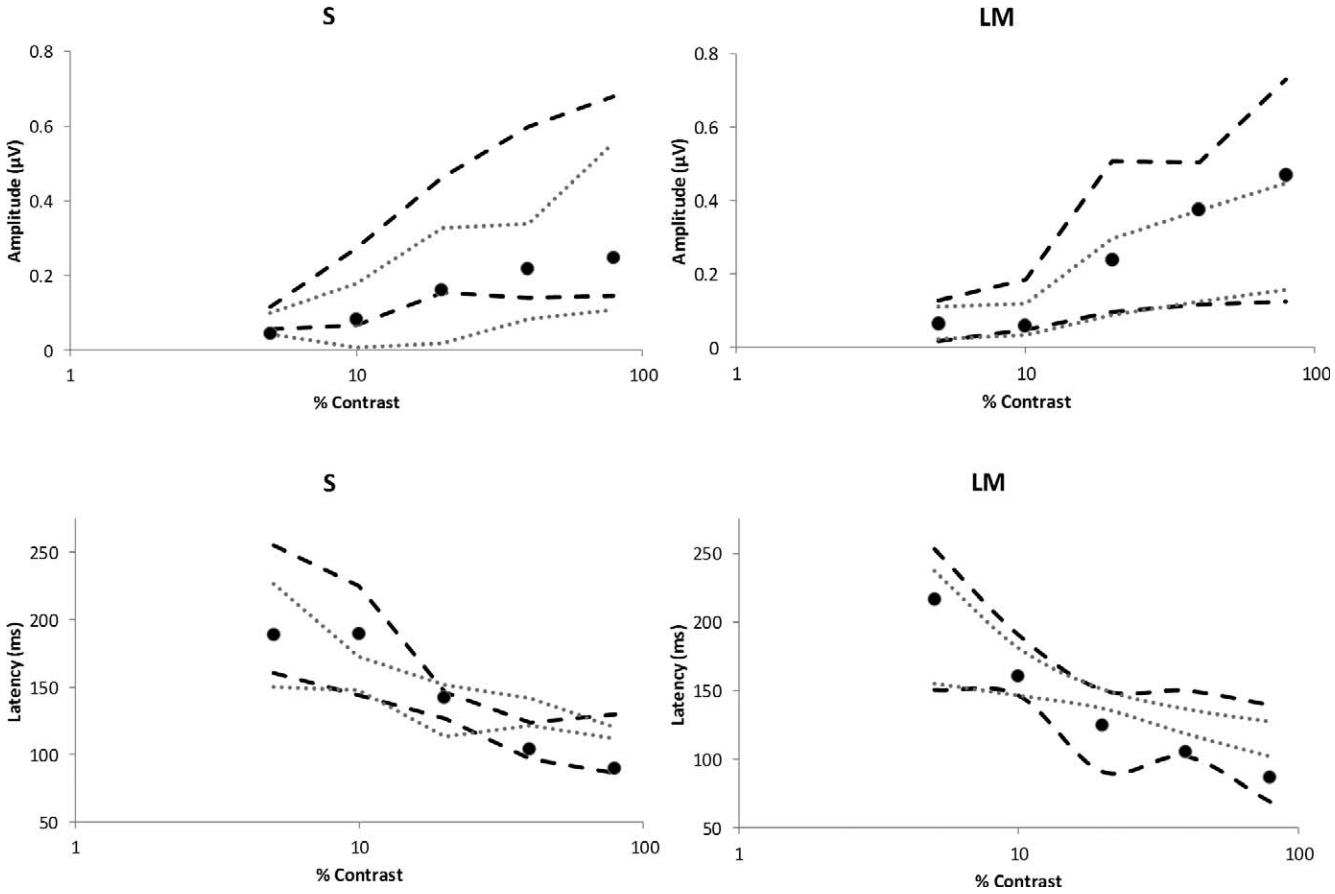

Figure 5. Amplitudes (top) and latencies (bottom) of the chromatic VEP as a function of contrast for subject MC1 (filled circles). Also shown are the ranges of amplitudes and latencies for all controls (dashed lines) and age-matched controls (dotted lines).

deficiencies that are precortical in origin (e.g., Crognale, Rabin, et al., 1993), *MC1's response amplitudes fall within or exceed the range of those of the normal observers at all contrasts*. This remains the case even when comparing her with the significantly younger control group.

Figure 5 (bottom panels) shows the contrast-response latency functions using S (left) and L-M (right) stimuli. The functions were constructed using the latency of the large negative component as measured from stimulus onset. As in the top panels, the range of response latencies from the two control groups is also indicated. The functions from MC1 show a typical decrease in latency with increasing contrast. Although prolonged latencies are indicative of both inherited and acquired color vision deficiencies of precortical origin (e.g., Crognale, Rabin, et al., 1993), MC1's response latencies are not unusually long and, in fact, are shorter than the mean of the normal population. As with amplitudes, this is true even for the nonage-matched group even though the average age was significantly younger. Results from both amplitude and latency measures suggest that MC1's color losses are not reflected in the cVEP and must reside beyond the generator of the major negative component of the cVEP in the visual stream. In short, MC1's contrast-response amplitude functions are remarkably normal.

Discussion and conclusions

The results presented above illuminate several interesting points regarding the cortical processing of color vision and the physiological substrate of color sensation. The cortical lesion of subject MC1 resulted in profound losses in her color sensation and capacity. The individual tests of color discrimination revealed various problems with her color vision, including discrimination (e.g., plate tests, CCT, FM-100) and color identification (e.g., Farnsworth lantern test). Surprisingly, the evoked potentials show essentially normal isolated opponent color responses as reflected in the waveforms of the chromatic VEP despite the significant loss of color capacities and self-described desaturation of the color sensation. These results are in accord with those reported by Setälä and Vesti (1994) and by Adachi-Usami et al. (1995), who employed pattern-reversal stimuli that are less optimized to selectively activate the chromatic channels (e.g., Mur-

ray et al., 1987; Rabin et al., 1994). In addition, participant MC1 exhibited normal contrast response functions for the VEP response without an obvious anomaly in response gain as contrast increased. This was true for both response amplitudes and latencies. This is particularly notable because latencies are known to be sensitive to more common color deficiencies (e.g., Crognale, Rabin, et al., 1993; Crognale, Switkes, et al., 1993; Rabin et al., 1994). Taken together, these results strongly suggest that the site of the generator of the chromatic pattern VEP lies prior in the processing stream to the site at which color sensation arises.

Results from fMRI (e.g., Engel et al., 1997; McKeefry & Zeki, 1997; Hadjikhani et al., 1998; Wandell et al., 2000; Wade et al., 2008; Cavina-Pratesi et al., 2010) and studies of patients with cerebral achromatopsia (e.g., Adachi-Usami et al., 1995; Bouvier & Engel, 2006) suggest ventral occipitotemporal areas (e.g., V4) as regions likely to have a selective role in color processing. The location of the lesion in the present study (ventral occipitotemporal cortex) includes these regions and is therefore consistent with these prior conclusions. MC1's brain lesion resulted not only in dyschromatopsia, but also several other deficits of function, such as prosopagnosia, spatial agnosia, and some memory deficits. Thus, it is likely that the lesion was not confined solely to areas that may have selective color function. Indeed it is not known with certainty whether or not there are cortical areas devoted solely to color processing or sensation. It is also not known with certainty which early cortical site gives rise to the cVEP. However, it appears from the results of the present study that the generator of the cVEP may not be homologous to those regions in the ventral occipital cortex identified as color selective by fMRI. In addition, it can be concluded that feedback from regions responsible for the sensation of color is not necessary for normal responses at the cortical level of the cVEP. And finally, we can deduce that normal responses from lower cortical areas to selective chromatic stimulation are not sufficient to produce the normal sensation of color.

Keywords: dyschromatopsia, cerebral achromatopsia, VEP

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