

Behavioral Deficits and Cortical Damage Loci in Cerebral Achromatopsia

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Lesions to ventral occipital cortex can produce severe deficits in color vision, a syndrome known as cerebral achromatopsia. Because most studies examine relatively few cases, however, uncertainty remains about precisely which cortical loci, when damaged, produce the syndrome. In addition, the extents of the associated perceptual deficits remain unclear. To address these issues, we performed a meta-analysis of 92 case reports from the literature. The severity of color vision deficits of the cases varied greatly, although nearly all showed some deficit in color discrimination. Almost all cases tested also showed some loss of spatial vision. Lesion overlap analyses revealed a relatively small region of high overlap in ventral occipital cortex. The region of high overlap was located near areas identified by neuroimaging studies as important for color perception. For comparison, we performed a similar analysis of prosopagnosia, a disorder of face perception, and found several regions of high lesion overlap adjacent to the region associated with achromatopsia. Because the behavioral deficits in achromatopsia are often incomplete and never restricted to color vision, the region of high lesion overlap may be one critical stage within a stream of many visual areas that participate nonexclusively in color perception.

Keywords: color, dyschromatopsia, lesions, prosopagnosia, vision

Introduction

Whether the primate brain contains a small region of extrastriate cortex specialized for color processing has remained controversial (Lueck *et al.*, 1989; Schiller and Lee, 1991; Zeki *et al.*, 1991; Heywood *et al.*, 1992; Walsh *et al.*, 1993; Tootell and Hadjikhani, 2001). Studies of human patients have provided perhaps the strongest evidence for such a color center. After an historical controversy (for a review, see Zeki, 1990), cases in which cortical damage can lead to disturbed color vision, a disorder termed achromatopsia, have come to be widely accepted. To date, however, analysis of achromatopsia rests mostly on single case reports, often with extensive cortical damage. The few reviews of more than a handful of cases have not conducted any quantitative analyses (Meadows, 1974; Zeki, 1990). Because of these limitations, the achromatopsia literature remains difficult to interpret. To examine more thoroughly the nature of achromatopsia, we cataloged the behavioral deficits and lesion anatomies of a large number of cases. For comparison, we collected cases with damage leading to a different disorder, prosopagnosia.

Materials and Methods

Identification and Selection of Cases

To identify cases of achromatopsia, we first performed literature searches in the PubMed database using as keywords all combinations

of one term from the group {'central', 'cerebral', 'cortical'} and one from the group {'achromatopsia', 'dyschromatopsia', 'color blindness'}. The search term used to collect prosopagnosia cases was 'prosopagnosia'. The case reports were then screened to remove cases with developmental or pre-cortical defects. The reference lists of relevant reviews and case reports were thoroughly examined to identify further articles. Abstracts from conference proceedings were not collected, as they were not likely to contain detailed case descriptions. Reports prior to 1970 and some unobtainable non-English reports were also excluded.

Tabulation of Behavioral Measurements

Results of behavioral tests were tabulated and categorized by hand. Behavioral abilities were never categorized as either present or absent unless a test was explicitly mentioned. For example, some reports of achromatopsia made no mention of face recognition. Such cases may have had intact face recognition, but for lack of certainty their abilities were categorized as 'unknown'. The full tabulation of test results used in our analyses is provided as Supplementary Table 1.

Lesion Overlap Analysis

Cases were included in the lesion overlap analysis that had: (i) CT, MRI or hand-drawn images in horizontal sections; (ii) clearly visible lesions; and (iii) identifiable brain landmarks. These criteria excluded some early cases whose CT or MRI images were noisy or showed only coronal slices. Note that the behavioral results of the excluded cases were nevertheless included in the tabulation described above.

We collected images of cases satisfying these criteria from published reports, and scanned them into a computer at high resolution. Lesions were then hand-traced onto a digital brain atlas (Woods *et al.*, 1999) that was rendered at multiple orientations allowing tracing to occur at the orientation shown in the case report. The traced slices were rotated to a common orientation using the AIR software (Woods *et al.*, 1998) and were projected to a single horizontal plane. We then calculated the number of cases with a lesion directly above or below each location in the projection plane. These numbers were rendered as an image superimposed on the atlas image at the average horizontal location of all lesions included in the analysis.

To compare lesion overlap results with the results of functional imaging studies, the coordinates of reported functional activation peaks were linearly transformed from Talairach space to the digital brain atlas space. The locations of the functional activations were then plotted on the overlap image.

We measured the focality of the lesion overlap by calculating the size of the overlap regions that were covered by a given percentage of the total number of lesions (e.g., the number of pixels that were in at least 50% of the lesions that produced achromatopsia). We then graphed the size of these overlap regions as a function of the number of lesions in the overlap. To generate error bars on these plots, subsets of the achromatopsia patient population were randomly resampled. Subsets of eight subjects were randomly selected without replacement, and the size of the overlap region was computed for each subset. The error bars represent the 5th and 95th percentiles of the distribution of overlap region sizes for each overlap percentage.

Results

Identification of Cases

The searches of achromatopsia terms yielded 722 hits. After screening for developmental and pre-cortical deficits, 42 articles remained. Of these, two were excluded because the disorder was of color constancy (Clarke *et al.*, 1998; Ruttiger *et al.*, 1999). Three were excluded as unobtainable foreign language papers; two were excluded as unobtainable papers more than 25 years old. The remaining 35 papers contained reports of 38 unique cases of achromatopsia. Of the 38 cases, 17 were diagnosed with prosopagnosia.

The PubMed search of keyword 'prosopagnosia' returned 347 articles. After screening for developmental and pre-cortical deficits, 136 articles remained. Of these, 44 were excluded as unobtainable foreign language papers; 46 were excluded as unobtainable papers more than 25 years old. The remaining 46 papers contained reports of 73 cases of prosopagnosia. Of the 73 cases, 38 were diagnosed with achromatopsia.

Taken together, the searches produced 76 cases of achromatopsia and 90 cases of prosopagnosia. We next reviewed all papers in the reference lists of the included papers. This review identified an additional 15 papers containing 16 cases of achromatopsia and 10 cases of prosopagnosia. This increase was likely due to the choice of keywords of some papers not including diagnostic descriptions (e.g. Clarke *et al.*, 1997). In total, we identified 92 cases of achromatopsia and 100 cases of prosopagnosia, which are listed in Appendix I and tallied in Supplementary Table 1. Note that these are not, 192 separate cases, as many patients have both disorders.

Color Vision Deficits

Most of our collected cases of achromatopsia were given one or more of three types of color vision tests: color naming, the Ishihara isochromatic plates, or the Farnsworth–Munsell 15- or 100-hue test. Overall, achromatopsics' deficits in color vision span a broad range of severity.

Color naming is the most commonly reported test of color vision, with 51% of cases tested (47 of 92 cases tested, hereafter denoted $n_{\text{tested}} = 47$ and $n_{\text{total}} = 92$). Typically, subjects are asked to name the color of paper patches or pieces of string. Remarkably, 49% of cases tested for color naming were able to perform normally ($n_{\text{tested}} = 47$). This percentage should be treated cautiously, however, because in some reports, naming tests were conducted informally, were not described or involved naming the colors of common objects which could be performed from memory rather than perception (e.g. Green and Lessell, 1977; Adachi-Usami *et al.*, 1995).

The Ishihara plates were also commonly used to test achromatopsics (48% of achromatopsics, $n_{\text{total}} = 92$). The test is most often used to screen for red-green colorblindness of peripheral origin in non-injured subjects. To pass the test, subjects must segregate isoluminant colored circles to identify the letter they form. Of the cases tested with Ishihara plates, 29% read them normally [three or fewer errors (Birch, 1997), $n_{\text{tested}} = 44$].

The Farnsworth–Munsell 100-hue test, and its 15-hue variant, have been administered to achromatopsics about as often as the other tests (50%, $n_{\text{total}} = 92$). Subjects arrange colored disks to continuously vary in hue. The tests detect deficits in color discrimination generally, and also identify common peripheral

defects. The worst performing 5% of the normal population scores between 80 and 195 depending upon age (Kinnear *et al.*, 2002). Achromatopsics' scores ranged from 106 to 1245, with a mean of 582, and none showed patterns typical of dichromatic or color anomalous observers. Very few of the achromatopsic patients performed at chance, however, which corresponds to a score of ~1200 (Victor, 1988). Thus, achromatopsics show a wide variety of performance in color discrimination, from near normal to total impairment.

The Nagel anomaloscope, which provides another method for evaluating color deficits, has been used to evaluate only a handful of cases ($n_{\text{tested}} = 8$). In this test, subjects manipulate the red-green content of a test field to match a given yellow field. Normal subjects select a unique red-green combination, while subjects with impaired red-green color vision accept many different red-green combinations as providing an adequate match. Of the tested cases, three performed normally and five performed abnormally. Two of the cases with abnormal performance were consistent with the performance of individuals with peripheral defects in color vision (Young and Fishman, 1980; Rizzo *et al.*, 1993).

Spatial Vision Deficits

The spatial vision of achromatopsic patients has only rarely been subject to thorough testing. Only 32% ($n_{\text{total}} = 92$) of cases report any test of spatial vision at all, and in most of these (67%, $n_{\text{tested}} = 29$) acuity is the only measure reported. The mean acuity of the cases tested was 0.85, roughly equivalent to 20/24 vision. Some isolated tests of spatial vision were also given, such as figure-ground segregation (Whiteley and Warrington, 1977), stereo fusion (Pearlman *et al.*, 1978), visual evoked potentials while viewing gratings (Bartolomeo *et al.*, 1997), dot counting (Orrell *et al.*, 1995) or reading (Pearlman *et al.*, 1978). Performance in all of these cases was described as normal. Also, many cases were given object recognition tests, likely to rule out object agnosia, and this type of test can also be a crude measure of spatial vision. Most subjects showed little deficit in object recognition (see Other Visual Disorders, below).

Of the few papers reporting thorough psychophysical testing of spatial vision, most found spatial deficits. One case was impaired at discrimination of illusory borders and Glass patterns (Gallant *et al.*, 2000). Another case was impaired at object naming and luminance contrast sensitivity (Merigan *et al.*, 1997), and another was impaired at texture discrimination (Mendola and Corkin, 1999). One well-studied case that showed normal acuity (Mollon *et al.*, 1980) nevertheless showed abnormal luminance contrast sensitivity (Heywood *et al.*, 1991; Kentridge *et al.*, 2004). However, one case exhibited normal contrast sensitivity, at least when tested at mid- to low-spatial frequencies (Rizzo *et al.*, 1992).

Other Visual Disorders

Several other visual disorders frequently co-occur with achromatopsia. Prosopagnosia co-occurs very often; fully 72% of cases with achromatopsia also have prosopagnosia ($n_{\text{total}} = 92$). Co-occurrence with other visual disorders, while less frequent, is still common: alexia co-occurs at a rate of 13%, spatial or topographical agnosia at 12%, and object agnosia at 8%.

Topography of Color Loss

Partial field color loss is relatively common; in our sample of cases, seven had a hemifield color loss (Albert *et al.*, 1975;

Damasio *et al.*, 1980; Freedman and Costa, 1992; Paulson *et al.*, 1994; Silverman and Galetta, 1995; Short and Graff-Radford, 2001) and six had a quarter-field color loss (Kolmel, 1988; Merigan *et al.*, 1997; Gallant *et al.*, 2000; Uttner *et al.*, 2002; Mesad *et al.*, 2003). Three cases of quarter-field color loss had the extent of their color vision rigorously mapped, and each had clear perceptual boundaries at the vertical and horizontal midlines (Kolmel, 1988; Merigan *et al.*, 1997). Of the six total cases of quarter-field color loss, four were localized to the superior left quadrant, one to the superior right quadrant and one to the inferior left quadrant (although the presence of an upper left visual field scotoma in this one case of left inferior quadrant color loss is also consistent with hemifield color loss).

All of the partial-field color losses with known lesion locations arose from unilateral lesions ($n_{\text{tested}} = 12$). In one case of hemifield color loss, whether the lesion was lateralized was unknown (Freedman and Costa, 1992). In only one case did a unilateral lesion lead to a full-field color impairment (Setala and Vesti, 1994). Of the remaining cases, 10 had unilateral lesions and unknown extents of color loss, and 51 had bilateral lesions, and most likely full-field color losses, though the spatial extent of the loss is seldom mentioned (Bartolomeo *et al.*, 1997; Beauchamp *et al.*, 2000). There were 17 cases with unknown lesion laterality and unknown extents of color loss.

Scotomas and Lesion Location

Cases of achromatopsia are commonly accompanied by scotomas—severe vision loss in part of the visual field. Figure 1 summarizes the locations of the scotomas reported in our sample of patients. For comparison, the figure also shows the scotomas of our identified cases of prosopagnosia (identified in a separate literature search—see Materials and Methods). The vast majority of the entire set of cases with either disorder (72%; $n_{\text{tested}} = 98$) had an upper visual field loss. The visual field losses of the achromatopsic and prosopagnosic populations

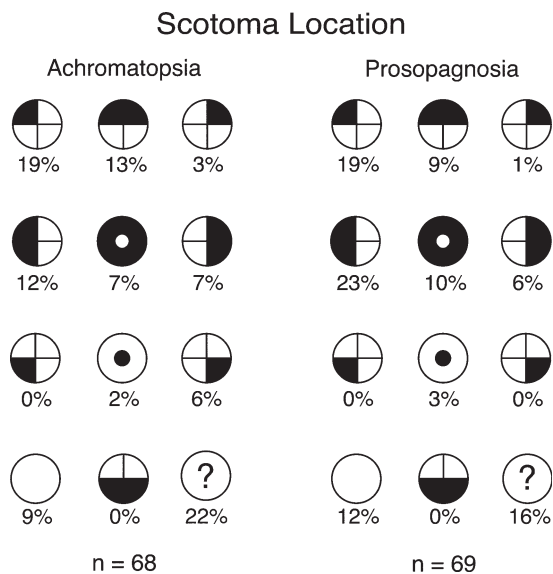


Figure 1. Scotoma locations. Scotomas are common in cases of achromatopsia and prosopagnosia. Shown are the percent of cases of achromatopsia and prosopagnosia with scotomas in the shaded location. The empty circle indicates cases with no scotomas, and the circle with the question mark indicates cases with scotomas that did not fit this categorization.

were similar in most respects, except the scotomas in prosopagnosia were more likely to be located in the left visual field.

Most of the cases with either disorder had bilateral lesions, but of those with unilateral lesions the majority were in the right hemisphere. Of achromatopsia cases with reported lesion laterality, 70% were caused by bilateral lesions, 20% were caused by a unilateral right lesion and 10% were caused by a unilateral left lesion ($n_{\text{tested}} = 70$). The distribution of lesions leading to prosopagnosia was similar, but perhaps more lateralized, with 65% bilateral, 32% unilateral right and 3% unilateral left lesions ($n_{\text{tested}} = 48$).

Lesion Overlap Analyses

Figure 2A shows the anatomical overlap of all patients with achromatopsia ($n_{\text{tested}} = 46$) and of all patients with prosopagnosia ($n_{\text{tested}} = 52$). Both images contain a well-defined, common region of high overlap in occipitotemporal cortex. This result was expected, since the most patients in our sample have both disorders. The common region of high overlap may very well contain separable sub-regions when damaged lead to each syndrome alone. Alternatively, since some vascular locations are more likely to be damaged (Osborne, 1991), the common region may simply represent a cortical location near a susceptible vascular location.

To test for the existence of sub-regions associated solely with achromatopsia, we analyzed the much smaller population of

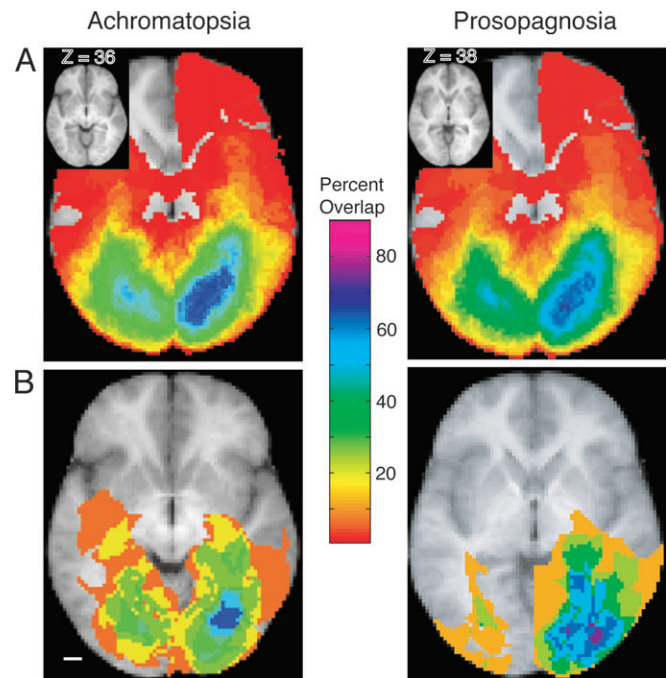


Figure 2. (A) Lesion overlap of all achromatopsia and prosopagnosia cases. The achromatopsia lesion overlap (left) contains lesions from all cases with achromatopsia regardless of prosopagnosia diagnosis ($n = 46$). The prosopagnosia lesion overlap (right) contains lesions from all cases with prosopagnosia regardless of achromatopsia diagnosis ($n = 52$). The inserts show the atlas anatomy (see Materials and Methods) and Talairach Z-coordinate at the average axial slice location for each group of cases. The lesion overlaps in Figure 4 are on the same anatomical slices. (B) Lesion overlap of achromatopsia and prosopagnosia cases with single disorder. The achromatopsia lesion overlap (left) contains lesions from only cases of achromatopsia and intact face processing ($n = 11$). The prosopagnosia lesion overlap (right) contains lesions from cases of prosopagnosia and intact color processing ($n = 8$). The scale bar indicates 1 cm.

patients who were clearly identified as having a deficit in color vision but intact face recognition. The overlap of cases with achromatopsia but not prosopagnosia is shown in Figure 2B (left). The large region of maximum overlap is in the right hemisphere, where 7 of 11 achromatopsia cases had lesions, with a center of mass at [30 -73 -2]. Within this region, there are two small locations where 8 of the 11 achromatopsia cases had lesions (Talairach coordinates [22 -74 36] and [28 -68 36]). Only 3 of 8 cases with prosopagnosia and intact color perception had lesions at the first location and 4 of 8 cases at the second location.

The three cases that fail to overlap with the rest of the achromatopsics are all cases with unilateral left hemisphere lesions. Mirroring the unilateral left hemisphere lesions to the right hemisphere increased the amount of overlap; one of the three lesions fell partially within the region of maximum overlap. Of the two cases that failed to overlap after mirroring their unilateral left hemisphere lesion into the right hemisphere, both were relatively close to the maximal region: one lesion was 2 mm and the other was 34 mm from its boundary.

The overlap analysis of cases with prosopagnosia but not achromatopsia is shown in Figure 2B (right). There are two regions of maximum overlap in the right hemisphere, where 6 of 8 prosopagnosia cases have lesions. The larger of the two is located slightly lateral and posterior to the area of maximum achromatopsia lesion overlap, with a center of mass at [33 -84 2]. The smaller of the two is located slightly medial and posterior to the area of maximum achromatopsia overlap, with a center of mass at [18 -81 2]. Achromatopsia cases had lesions at the center of mass of the lateral site in 3 of 11 cases and of the medial site in 4 of 11 cases. As in the achromatopsia analysis, one of the cases that failed to overlap was the result of a unilateral left hemisphere lesion. Mirroring the one unilateral left hemisphere lesion to the right hemisphere increased the amount of overlap; all of the eight subjects' lesions overlap with either the medial region or the lateral region.

Overlap of Achromatopsia Lesions is More Focused

Figure 3 shows a comparison of the size of overlap regions for prosopagnosia and achromatopsia as a function of the number of cases overlapping. The y -axis indicates the size of the overlap region, given a criterion amount of overlap. The x -axis indicates this criterion amount of overlap, measured as a percentage of the total cases included in the analysis. For example, the size of the region of overlap that contains 50% of the cases of achromatopsia is 634 mm². At overlap percentages of 50 and 62.5%, the overlap of lesions that cause achromatopsia is reliably smaller than the overlap of lesions causing prosopagnosia. We computed error bars for the sizes of the achromatopsia overlap regions using a resampling procedure (see Materials and Methods).

Comparison to Imaging Results

Figure 4 superimposes on the lesion analyses peak activations from imaging experiments that have attempted to isolate color or face-related activity. The left panel shows the peak activations from studies of color vision superimposed on the achromatopsia lesion overlap (McKeefry and Zeki, 1997; Hadjikhani *et al.*, 1998; Beauchamp *et al.*, 1999; Bartels and Zeki, 2000). In cases where multiple activations are reported, the anterior location of the activation is plotted in red, and the posterior location is plotted in black. In all cases, the peak activations

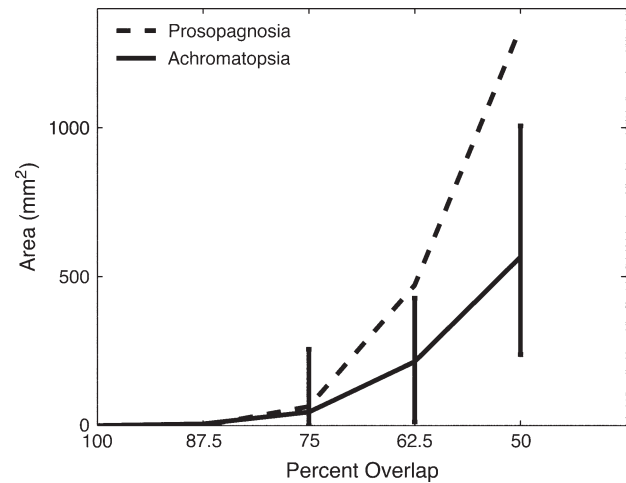


Figure 3. Achromatopsia and prosopagnosia lesion overlap sizes. Lesion overlaps from cases with achromatopsia and intact face processing were compared to lesion overlaps from cases of prosopagnosia and intact color processing at several different criterion levels. Error bars on achromatopsia lesion sizes were estimated by resampling the achromatopsia cases in groups of eight, to match the number of prosopagnosia cases. At criteria of 50 and 62.5% overlap, the overlap of lesions causing achromatopsia is smaller than the overlap of lesions causing prosopagnosia.

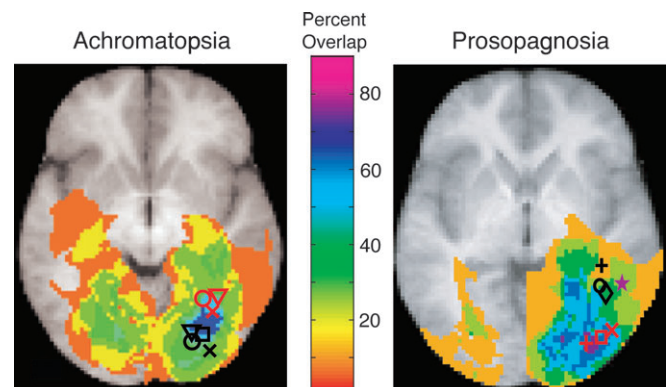


Figure 4. Lesion overlaps with neuroimaging results. Achromatopsia and prosopagnosia lesion overlaps are shown with representative neuroimaging peak activations superimposed. On achromatopsia lesion overlap (left), black symbols indicate posterior color-sensitive findings and red symbols indicate anterior color-sensitive findings in studies reporting multiple responses. On prosopagnosia overlap (right), black symbols indicate responses near the face-sensitive area FFA, red symbols indicate responses near the face-sensitive area OFA, and the purple symbol indicates a response near the face-sensitive area STS. Achromatopsia references: circle, Beauchamp *et al.* (1999); X, Hadjikhani *et al.* (1988); triangle, Bartels and Zeki (2000); square, McKeefry and Zeki (1997). Prosopagnosia references: +, Haxby *et al.* (1994); circle, Halgren *et al.* (1999); diamond, Kanwisher *et al.* (1997); X, Rossion *et al.* (2003b); square, Rossion *et al.* (2003a); star, Puce *et al.* (1999).

fall reasonably close [within 64 mm (mean = 18.4 mm)] to the region of maximum lesion overlap.

Figure 4 also plots locations of peak activations from neuroimaging studies of face processing superimposed on the prosopagnosia lesion overlap. Activations are plotted for three important face-processing areas: the fusiform face area (FFA) in black; the occipital face area (OFA) in red; and the superior temporal sulcus (STS) in purple (Haxby *et al.*, 1994; Kanwisher *et al.*, 1997; Halgren *et al.*, 1999; Puce *et al.*, 1999; Rossion *et al.*, 2003a,b). Peaks reported in the OFA fall closer to regions of maximum lesion overlap than peaks in the FFA or the STS.

Discussion

A Region of High Lesion Overlap in Achromatopsia

Our analysis shows that a relatively small, critical region in cortex is damaged in almost every known case of achromatopsia. The size of this region is reliably smaller than a comparable region associated with prosopagnosia. The simplest explanation of our results is that color perception depends upon the intact function of a small region of cortex. Our lesion data are not precise enough, and the functional imaging results not well enough agreed upon, to determine whether the critical region intersects only a single visual area; it appears close to the reported locations of putative areas V4v, V8 and V4 α (see below). Our results agree with those from previous studies that have compared the locations of multiple cases of achromatopsia (Short and Graff-Radford, 2001; Tanaka *et al.*, 2002), though no other studies have included formal analysis of lesion overlap with large numbers of cases.

The localization of the scotomas associated with the cases of achromatopsia is consistent with the ventral location of the critical region. Upper field scotomas are by far the most common type, as has been noted here and by others (e.g. Meadows, 1974). These scotomas are most likely the result of injury that extends into V1 or the optic radiations, as both of these structures represent the upper visual field on their ventral surface.

Correspondence with Visual Areas

The location of the critical region of lesion overlap aligns well with areas identified in functional imaging studies. Initial studies (Lueck *et al.*, 1989; Zeki *et al.*, 1991) reported an area located on the ventral surface of the occipital cortex specialized for color vision. Many other neuroimaging experiments that attempted to localize color-selective responses report peak activations in this same general region (McKeefry and Zeki, 1997; Zeki and Marini, 1998; Beauchamp *et al.*, 1999; Bartels and Zeki, 2000). One experiment that simultaneously localized color- and face-selective responses (Clark *et al.*, 1997) reported activations consistent with the critical regions identified here: performance on a color task was associated with a location near the critical region of lesion overlap in achromatopsia, and performance on the face task was associated with a more variable region lateral to the color responsive region.

Measurements of retinotopic organization showed that the color selective area represents a visual hemifield (McKeefry and Zeki, 1997; Hadjikhani *et al.*, 1998; Wade *et al.*, 2002). Recently, a debate has developed regarding whether an additional quarter-field representation exists between it and ventral area V3 (also called VP) (Hadjikhani *et al.*, 1998; Bartels and Zeki, 2000; Wade *et al.*, 2002). Our region of maximum overlap in achromatopsia falls close to the reported locations of both the original color area and the proposed quarter-field area.

The visual field topography of color vision deficits also constrains the identity of the damaged visual areas. The part of space represented is almost certainly restricted to one half of the visual field, since almost all cases of achromatopsia from unilateral lesions had spared color vision in at least the contralateral hemifield [there is one reported case of full-field color loss from a unilateral lesion (Setala and Vesti, 1994)]. The presence of crisp quarter-field color impairments further suggests that in some cases the damaged area or areas may

represent only that portion of visual space. While partial damage to a hemifield representation could in principle produce something like a quarter-field deficit, the likelihood of it producing color loss that completely and exclusively fills a quarter of the visual field is vanishingly small. Thus, there are likely to be visual areas with both quarter- and hemifield representations within the regions of maximum overlap.

Specialization for Color Vision

Overall, there is little doubt that the region that is damaged in cases of achromatopsia is important for color vision. Many of the cases in our sample were impaired at color naming and at recognizing the Ishihara plates. Nearly all of the cases showed some degree of deficit when tested with the Farnsworth-Munsell 100-hue test or its 15-hue variant. Of the two cases approaching normal scores on this test, one recovered within one month (Nakadomari *et al.*, 1999) and the other recovered within two years (Beauchamp *et al.*, 1999). In all, the mean error score for this group was 582, well outside the range of normal performance (Kinnear and Sahaie, 2002).

Frequently, the loss of color vision is far from complete. Many of the cases can perform at normal levels on some tasks: 49% can adequately name or match colors, while 29% have enough residual chromatic vision to read the Ishihara plates within the normal limits. One case was able to read the plates when they are displayed at a greater distance (2 m), but not at reading distance (Mollon *et al.*, 1980). This may be an example of residual chromatic processing when the task takes on a figure-ground aspect at greater viewing distances. Performance on the Farnsworth-Munsell 100-hue test is also better than chance (Victor, 1988) for most cases tested. Partially spared color vision in many of these cases is in agreement with reports of lesion studies in monkeys, where ablations in the inferior occipitotemporal lobe, near the visual areas collectively known as IT, cause deficits similar to human achromatopsia (Heywood *et al.*, 1988, 1995; Huxlin *et al.*, 2000). Damage to macaque IT cortex can result in chromatic deficiencies that are either mild (Huxlin *et al.*, 2000) or profound (Heywood *et al.*, 1995).

There is little evidence, apart from broad measures of acuity, that the region damaged in achromatopsia is exclusively devoted to color vision. When spatial vision was tested in more detail, substantial deficits were consistently found. Lesions in non-human primates have produced similar deficits; monkeys with bilateral IT lesions are at least mildly impaired at spatial tasks, including, for example, illusory contour detection (Huxlin *et al.*, 2000), shape matching (Merigan and Saunders, 2004) and achromatic discrimination (Heywood *et al.*, 1995). For reasons that remain unclear, however, spatial deficits are smaller or non-existent in animals with unilateral IT lesions (Merigan and Saunders, 2004).

Some caution is warranted in interpreting our results. First, interpretation of the behavioral data is difficult because negative results of tests are likely underreported, hindering inferences about general rates of behavioral deficits. Even when tests are reported, they are often not well described, making detailed evaluation of behavioral deficits impossible except in a handful of cases. Second, the lesion overlap analysis was very limited in its scope. We used only axial images of brain anatomy, which narrowed the sample size and caused a loss of information about overlap in the *z*-dimension. The analysis also used only the anatomical slices shown in the case reports. These probably

gave a biased sense of lesion location; for example, few cases show axial images lesions along the ventral surface of occipito-temporal cortex, for the understandable reason that such images have few identifiable landmarks and are difficult to interpret. Finally, and probably most critically, our sample of cases was biased in that it only included patients diagnosed with prosopagnosia or achromatopsia. Our review points to the need for a large prospective study of patients with occipito-temporal lesions, where cases are selected based upon lesion location alone, and the accompanying behavioral deficits are tabulated.

Prosopagnosia

Unlike the results from the analysis of the achromatopsia cases, the anatomical analysis of prosopagnosia cases did not yield a single, contiguous region of maximum overlap. Instead, there were several non-contiguous regions that were lesioned in many cases. This result agrees well with other evidence for distributed face processing in cortex (Farah and Aguirre, 1999; Haxby *et al.*, 2001). There are several candidate face processing areas: the fusiform face area (FFA) (Kanwisher *et al.*, 1997), the superior temporal sulcus (STS) (Puce *et al.*, 1998) and the occipital face area (OFA) (Rossion *et al.*, 2003a). The cases reported here have lesions most often in the vicinity of the OFA. The relative infrequency of STS lesions producing prosopagnosia is not surprising, since this area responds to changes in facial expression or viewing angle (Haxby *et al.*, 2000). Deficits in processing such information might not be diagnosed as prosopagnosia. The lack of lesions near the FFA is more surprising, since other evidence indicates this area is important for face recognition (Haxby *et al.*, 1994; Kanwisher *et al.*, 1997; Halgren *et al.*, 1999; Rossion *et al.*, 2003a,b). However, there was a region of high lesion overlap located relatively close, though medial to the site of FFA activations (Fig. 4). The misregistration between the anterior overlap regions and the FFA might result from a bias in our sample of images. As mentioned above, the slices chosen for lesion illustration tend to avoid the ventral surface of the brain, where the FFA is located. The images used in our study were superior to the FFA, where cortex has curved around medially and the FFA's location contains white matter. Thus, lesions that contained the FFA as well as other more superior cortex would likely appear more medial in our analysis.

Conclusions: A Color Center?

Our results provide good evidence for a common region damaged in achromatopsia that is important for color vision. For there to be a single true color 'center', the damaged region should show three additional properties, however: (i) It should contain a single visual area; (ii) color vision should be the only perceptual ability it supports and (iii) color vision should not be critically dependent upon other late visual areas. Our results provide at least some reason to doubt whether each of these properties hold in cases of achromatopsia. First, the region of common overlap likely contains two retinotopically defined visual areas, one containing a quarter-field representation and one containing a hemifield representation. Second, the common region is also likely also important for spatial vision, since spatial deficits almost always co-occur with achromatopsia. Third, other late visual areas may play a significant role in color perception, since there is frequently substantial residual color vision even when the common region is damaged.

Our results agree with a less centralized view, in which color perception arises from a stream of processing that flows through multiple multipurpose visual areas. The many cases of partially spared color vision suggest that some visual areas outside the ones commonly damaged in achromatopsia participate in the color-processing stream. The frequency of deficits in spatial vision in cases of achromatopsia likely indicates that more than one type of information is processed in the damaged areas. Achromatopsia likely results from the lesion of one critical step in the many stages of processing that support color perception.

Notes

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Appendix 1

Case	Achromatopsia diagnosis	Prosopagnosia diagnosis	Anatomy available	Reference
Case 1	Present	Present	Yes	Adachi-Usami <i>et al.</i> (1995)
Case 1	Present	Unknown	No	Albert <i>et al.</i> (1975)
Case 1	Unknown	Present	No	Aptman <i>et al.</i> (1977)
Madame D	Present	Present	Yes	Bartolomeo <i>et al.</i> (1997)
KG	Present	Absent	Yes	Beauchamp <i>et al.</i> (2000)
Case 1	Present	Present	Yes	Brazis <i>et al.</i> (1981)
Mr W	Present	Present	Yes	Bruyer <i>et al.</i> (1983)
WM	Present	Present	Yes	Cavanagh <i>et al.</i> (1998)
JPC	Present	Present	No	Cavanagh <i>et al.</i> (1998)
JPN	Present	Present	No	Cavanagh <i>et al.</i> (1998)
Case 1	Present	Present	Yes	Clarke <i>et al.</i> (1997)
Case 2	Absent	Present	No	Clarke <i>et al.</i> (1997)
LM	Present	Present	No	Cowey and Vaina (2000)
CM	Present	Absent	Yes	Damasio <i>et al.</i> (1980)
EH	Present	Absent	Yes	Damasio <i>et al.</i> (1980)
Case 1	Present	Present	Yes	Damasio <i>et al.</i> (1982)
Case 2	Present	Present	Yes	Damasio <i>et al.</i> (1982)
Case 3	Unknown	Present	Yes	Damasio <i>et al.</i> (1982)
Case 1	Unknown	Present	Yes	De Renzi (1986)
Case 2	Unknown	Present	Yes	De Renzi (1986)
PA	Unknown	Present	Yes	De Renzi <i>et al.</i> (1994)
OR	Absent	Present	Yes	De Renzi <i>et al.</i> (1994)
LM	Unknown	Present	Yes	De Renzi <i>et al.</i> (1994)
Anna	Unknown	Present	Yes	De Renzi and di Pellegrino (1998)
CF	Present	Present	Yes	Dumont <i>et al.</i> (1981)
Case 1	Present	Absent	Yes	Duvelloy-Hommet <i>et al.</i> (1997)
Case 1	Present	Present	Yes	Ettlin <i>et al.</i> (1992)
VH	Unknown	Present	No	Evans <i>et al.</i> (1995)
Case 1	Present	Present	No	Freedman and Costa (1992)
CO	Absent	Present	No	Gainotti <i>et al.</i> (2003)
AR	Present	Absent	Yes	Gallant <i>et al.</i> (2000)
Case 1	Present	Present	No	Goldenberg <i>et al.</i> (1985)
Case 1	Present	Present	Yes	Gomori and Hawryluk (1984)
Case 1	Present	Unknown	Yes	Green and Lessell (1977)
Case 2	Present	Present	No	Green and Lessell (1977)
Case 3	Present	Present	No	Green and Lessell (1977)
Case 4	Present	Present	No	Green and Lessell (1977)
Case 5	Present	Absent	No	Green and Lessell (1977)
Case 1	Absent	Present	Yes	Habib (1986)
Case 1	Present	Present	No	Hoksbergen <i>et al.</i> (1996)
Case 1	Present	Unknown	No	Jaeger <i>et al.</i> (1989)
Case 1	Absent	Present	Yes	Kawahata and Nagata (1989)
Case 1	Present	Present	No	Kay and Levin (1982)
Case 2	Present	Present	No	Kay and Levin (1982)
Case 3	Present	Present	No	Kay and Levin (1982)
BL	Present	Present	No	Kennard <i>et al.</i> (1995)
Case 1	Present	Absent	Yes	Kolmel (1988)
Case 2	Present	Absent	Yes	Kolmel (1988)
Case 1	Unknown	Present	No	Kubo <i>et al.</i> (1978)
Case 1	Unknown	Present	Yes	Landis <i>et al.</i> (1986)
Case 2	Unknown	Present	Yes	Landis <i>et al.</i> (1986)
Case 3	Present	Present	Yes	Landis <i>et al.</i> (1986)
Case 4	Absent	Present	No	Landis <i>et al.</i> (1986)

continued

Appendix 1

continued

Case	Achromatopsia diagnosis	Prosopagnosia diagnosis	Anatomy available	Reference
Case 5	Absent	Present	No	Landis <i>et al.</i> (1986)
Case 6	Unknown	Present	No	Landis <i>et al.</i> (1986)
Case 1	Unknown	Present	No	Landis <i>et al.</i> (1988)
Case 1	Present	Present	No	Levine <i>et al.</i> (1985)
Case 1	Absent	Present	Yes	Lin and Pai (2000)
Case 1	Present	Present	No	Malone <i>et al.</i> (1982)
Case 2	Present	Present	No	Malone <i>et al.</i> (1982)
LM	Absent	Present	Yes	Marciani <i>et al.</i> (1991)
DN	Absent	Present	Yes	Mattson <i>et al.</i> (2000)
Case 1	Present	Absent	No	Meadows (1974)
Case 2	Unknown	Present	No	Meadows (1974)
Cases 3-14	Present	Present	No	Meadows (1974)
Case 1	Unknown	Present	No	Mendez and Ghajarnia (2001)
Case 1	Present	Present	Yes	Mendola and Corkin (1999)
RP	Present	Unknown	Yes	Merigan <i>et al.</i> (1997)
Case 1	Present	Present	No	Mesad <i>et al.</i> (2003)
84.00.503	Absent	Present	Yes	Michel <i>et al.</i> (1986)
MS	Present	Present	Yes	Mollon <i>et al.</i> (1980); Heywood <i>et al.</i> (1991)
Case 1	Present	Present	Yes	Nakadomari (1997)
Case 2	Present	Unknown	Yes	Nakadomari (1997)
Case 3	Present	Unknown	Yes	Nakadomari (1997)
Case 2	Present	Absent	Yes	Nakadomari <i>et al.</i> (1999); Tanaka <i>et al.</i> (2002)
Case 1	Present	Absent	Yes	Nakadomari <i>et al.</i> (1999)
AA	Present	Present	No	Nardelli <i>et al.</i> (1982)
OO	Present	Present	No	Nardelli <i>et al.</i> (1982)
GB	Present	Present	No	Nardelli <i>et al.</i> (1982)
FS	Unknown	Present	No	Nardelli <i>et al.</i> (1982)
MH	Present	Present	Yes	Ogden (1993)
Case 1	Present	Present	Yes	Orrell <i>et al.</i> (1995)
Case 1	Present	Absent	Yes	Paulson <i>et al.</i> (1994)
Case 2	Present	Absent	Yes	Paulson <i>et al.</i> (1994)
Case 1	Present	Present	Yes	Pearlman <i>et al.</i> (1978)
Case 1	Present	Present	Yes	Poppel <i>et al.</i> (1978)
89526	Present	Present	Yes	Pradat-Diehl <i>et al.</i> (1999)
PP	Present	Present	No	Rizzo <i>et al.</i> (1992, 1993)
Case 1	Present	Present	No	Rizzo <i>et al.</i> (1993)
Case 1	Present	Present	No	Ross (1980)
Case 1	Present	Unknown	Yes	Sakurai <i>et al.</i> (2001)
Case 1	Present	Present	No	Scarpattetti <i>et al.</i> (1983)
MT	Unknown	Present	Yes	Schweinberger <i>et al.</i> (1995)
Case 1	Present	Absent	Yes	Setala and Vesti (1994)
Case 1	Present	Unknown	No	Short and Graff-Radford (2001)
EH	Present	Absent	Yes	Shuren <i>et al.</i> (1996)
Case 1	Present	Absent	Yes	Silverman and Galetta (1995)
WL	Present	Present	Yes	Spillmann <i>et al.</i> (2000)
Case 1	Present	Present	Yes	Tagawa <i>et al.</i> (1990)
Case 1	Unknown	Present	Yes	Takahashi <i>et al.</i> (1989)
Case 1	Present	Present	Yes	Takahashi <i>et al.</i> (1995)
Case 2	Unknown	Present	No	Takahashi <i>et al.</i> (1995)
Case 3	Unknown	Present	Yes	Takahashi <i>et al.</i> (1995)
Case 4	Unknown	Present	Yes	Takahashi <i>et al.</i> (1995)
Case 1	Present	Unknown	Yes	Tanaka <i>et al.</i> (2002)
Case 3	Present	Present	Yes	Tanaka <i>et al.</i> (2002)
Case 4	Present	Present	Yes	Tanaka <i>et al.</i> (2002)
Case 1	Absent	Present	Yes	Tohgi <i>et al.</i> (1994)
Case 1	Unknown	Present	Yes	Uttner <i>et al.</i> (2002)
Case 2	Present	Absent	Yes	Uttner <i>et al.</i> (2002)
MS	Present	Present	Yes	Victor <i>et al.</i> (1989)
FW	Present	Present	No	Whiteley and Warrington (1977)
QL	Absent	Present	No	Whiteley and Warrington (1977)
WA	Present	Present	No	Whiteley and Warrington (1977)
Case 1	Present	Absent	No	Young <i>et al.</i> (1980)
PM	Present	Present	Yes	Young and Fishman (1980)

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