Retinotopy and color sensitivity in human visual cortical area V8

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Prior studies suggest the presence of a color-selective area in the inferior occipital-temporal region of human visual cortex. It has been proposed that this human area is homologous to macaque area V4, which is arguably color selective, but this has never been tested directly. To test this model, we compared the location of the human color-selective region to the retinotopic area boundaries in the same subjects, using functional magnetic resonance imaging (fMRI), cortical flattening and retinotopic mapping techniques. The human color-selective region did not match the location of area V4 (neither its dorsal nor ventral subdivisions), as extrapolated from macaque maps. Instead this region coincides with a new retinotopic area that we call 'V8', which includes a distinct representation of the fovea and both upper and lower visual fields. We also tested the response to stimuli that produce color afterimages and found that these stimuli, like real colors, caused preferential activation of V8 but not V4.

In Old World primates such as macaque monkeys and humans, visual information about color is processed in anatomically segregated columns, layers, channels or areas. It is important to know to what extent color is processed in separate versus convergent visual information pathways, because the added dimension of color is so rich in visual information. For example, we can discriminate about fifteen hundred different levels of luminance[1], whereas we can make several million discriminations if we also consider variations in color[2]. It is likely that this glut of color information is incorporated into the labeled lines of the neural architecture in some organized way.

In macaque monkeys, an anatomical segregation between chromatic-opponent versus achromatic-opponent cells has been reported as early as the lateral geniculate nucleus. Color-specific anatomical segregation has also been described in primary (V1) and secondary (V2) visual cortex. In V1, prominent populations of color-selective cells have been reported in specific layers[3–5] and in the cytochrome-oxidase blobs[4–6], though the latter claim has been disputed[7,8]. Similar (and equally controversial) claims have been made about the prominence of color-opponent cells in the 'thin' stripes in area V2, to which the V1 blobs project (ref. 9,10, but see 11).

However, the most prominent controversy about the anatomical segregation of color-selective neurons occurs at a higher level, in cortical area V4. According to different reports, a high percentage of color-selective cells is either present[12–15] or absent[16] in the largest and best-studied portion of that area, dorsal V4 (V4d). A high percentage of color-selective cells has not been reported in the smaller, ventral subdivision of V4 (V4v). More recent evidence suggests that brain mechanisms critical for color selectivity are located not in macaque V4, but rather in areas anterior to it (ref. 17–19, Vanduffel *et al. Soc. Neurosci. Abstr.* 23, 845, 1997).

This controversy about color selectivity in V4 has now been extended to human visual cortex. Based on human neuroimaging studies, a small patch of color-selective activity near the middle of the collateral sulcus has been named 'V4' (ref. 20–22). This choice of name presupposes that (1) an area homologous to macaque V4 exists in humans, (2) V4 is color-selective, and (3) this region in or near the collateral sulcus is the macaque V4 homolog. However, in humans, the location of this color-selective region has not yet been compared with the map of retinotopic areas, to see whether color selectivity is really is in a retinotopically defined human area V4. Furthermore, the degree of color selectivity in macaque V4 is itself controversial[17–19].

This issue is not just of academic interest. In an intriguing clinical syndrome ('achromatopsia'), human patients report that the visual world becomes colorless following damage to a cortical region that apparently includes this color-selective area in the collateral sulcus[23–25]. This suggests that the conscious percept of 'color' involves that area, although it is known that physical wavelength-dependent differences are coded throughout prior levels of the visual system as well. If we can define better which area this is in humans, we can learn something about where conscious perceptions of color arise. Accurate localization in humans should also make it possible to study the homologous area in macaques using more incisive (but invasive) classical neurobiological techniques.

We have attempted to clarify these issues in humans using functional magnetic resonance imaging (fMRI). Technical details were similar to those described elsewhere[26], except that here we manipulated the color content of the visual stimuli. We also used a high-field MRI scanner and other improvements to substantially increase the sensitivity of the retinotopic maps (Methods).

Results

Color- versus luminance-varying stimuli

First, we compared the activity produced by color variations to that produced by variations in luminance, in the same sub-

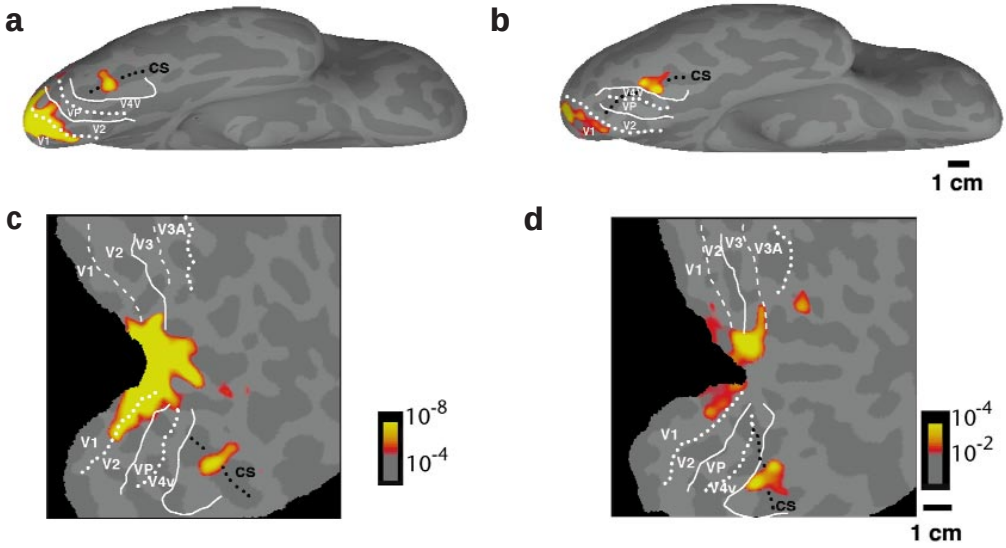

Fig. 1. Topography of color-selective activity in human visual cortex. **(a, b)** The inferior, 'inflated' cortex, with posterior to the left and anterior to the right, in two subjects. **(c, d)** The posterior portion of cortex in fully flattened format, another view of the same data shown in (a) and (b), respectively. In all panels, gyri from the original brain are shown as light gray and sulci as dark gray. The fundus of the collateral sulcus (cs) is indicated by the dashed black line. The borders of previously described retinotopic areas (V1, V2, V3, VP, V3A, and V4v) are indicated in white (horizontal meridians, solid lines, upper vertical meridians, dotted lines, lower vertical meridians, dashed lines). Typically, color-varying stimuli produced relatively higher activation in the foveal representation of V1 and often V2 and V3/VP and a distinctive patch of color-selective activation approximately midway in the collateral sulcus. When present, the latter patch was always located just anterior to the horizontal meridian representation marking the anterior border of area V4v, rather than within V4v.

jects (Fig. 1). Our stimuli consisted of slowly moving sinusoidal radial gratings ('pinwheels') of low spatial frequency, defined by either color or luminance contrast (Methods). As shown earlier in V1 and V2 (ref. 27), we found that both color- and luminance-varying stimuli produced robust activation in many areas of visual cortex, when compared with a uniform gray field (data not shown).

Here we focused on those locations where the color stimuli produced more activation than the luminance stimuli. In the classically retinotopic visual areas (V1, V2, V3/VP, V3A and V4v), we found prominent color-selective activation in the representations of the fovea (center of gaze) but not in peripheral representations (Fig. 1). A foveal color bias has not been reported in previous imaging studies, perhaps because it is more obvious in our flattened maps. However, such a foveal color bias is consistent with the well known predominance of cone photoreceptors, and the corresponding absence of rods, in the fovea of the retina. A similar foveal color bias is found in routine clinical perimetry and in numerous psychophysical studies.

In 25 of 26 hemispheres (13 subjects) tested, we found an additional region that responded preferentially to color, located midway along the length of the collateral sulcus. Based on the anatomical location and the nature of the functional comparison used here, this collateral color-selective patch appears equivalent to the previously reported area involved in achromatopsia[20,22], which has been proposed as the human homologue of macaque area V4 (refs 20–22, 28–30).

However, when we compared the location of that collateral color-selective patch to the retinotopic borders in the same subjects, we found that the color-selective patch was consistently located just beyond the most anterior retinotopic area defined previously, area V4v. Earlier reports[26,31–33] suggested that human V4v is a quarter-field representation of the contralateral upper visual field. The more sensitive retinotopic mapping

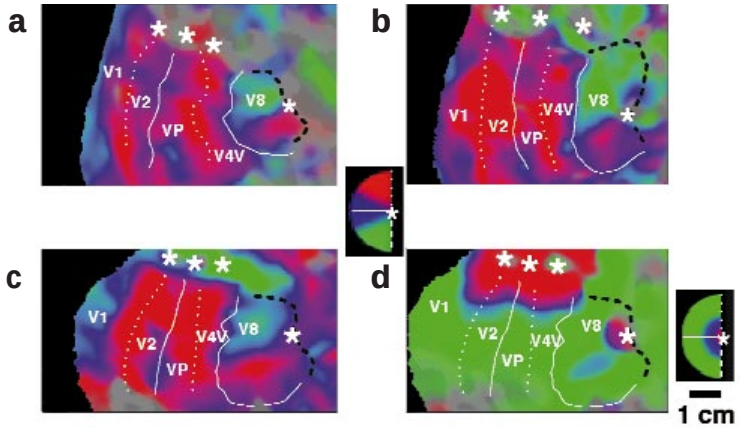

Fig. 2. Retinotopic features of area V8 by fMRI mapping. **(a–c)** Retinotopy of polar angle in the inferior row of cortical areas, from three flattened hemispheres. From left to right, each panel shows the representations of the contralateral upper quarter field (red through blue or vice versa; see pseudocolor logo) in inferior V1, then inferior V2, then VP, then V4v. To the right of (anterior to) V4v is the distinctive half-field representation comprising V8 (green through blue through red, from upper to lower in this figure). **(d)** Retinotopic representation of eccentricity (the other dimension in polar space), from the same hemisphere shown in (c). The representations of central-through-more-peripheral eccentricities are coded in red-through-blue-through-green, respectively (see pseudocolor logo, bottom right). The representations of the center of gaze are indicated with an asterisk. Area V8 has its own representation of the fovea, quite distinct (and 3.5 cm) from the foveal representation in adjacent area V4v.

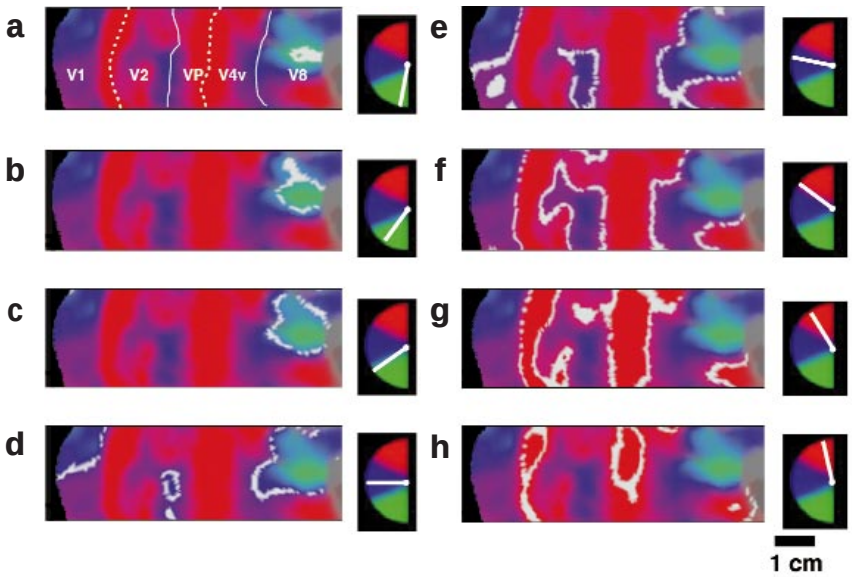

Fig. 3. Detailed retinotopy of the polar angle representation, from the same hemisphere shown in Fig. 2a. This figure shows the peak fMRI response (noisy white lines) corresponding to polar angle gradients of approximately 20°, superimposed on the standard pseudocolor rendering of areas V1, V2, VP and V4v (drawn in a). To the right of each panel is a logo indicating the specific polar angle (white line) stimulated. The complete contralateral visual field is represented in V8, from the lower visual field (**a** and **b**), across the horizontal meridian **(c–e)** to the upper visual field **(f–h)**. Note in (e–h) that the upper visual field representation in V8 can clearly be distinguished from, and is mirror symmetric to, that in adjacent V4v.

In conventional Talairach coordinates, foveal V4v (as defined retinotopically in this study) was centered at ± 32, -87, -16, whereas foveal V8 was centered at ± 33, -65, -14. When we averaged the Talairach coordinates of the color-selective area 'V4' described in previous studies (± 26, -67, -9), we found that it was about twice as close to the location of our retinotopically defined V8, compared to our retinotopically defined V4v. This supports all the other evidence that the color-selective activity is located in area V8, rather than in 'V4'.

In each hemisphere, V8 comprises a continuous representation of the entire contralateral half of the visual field. Although the authors did not attempt polar-coordinate retinotopy or flattened mapping, a prior study also concluded that this human color-selective region included a representation of upper and lower visual fields[22]. Together with V8 in the opposing hemisphere, the entire visual field is thus represented. Such a complete representation of the visual field would be appropriate in an area processing higher-order, large-field color information.

methods used here confirmed that V4v represents just that quarter field, with its foveal representation located superiorly alongside that of adjacent areas V3/VP (Figs 2 and 3).

The improved retinotopic methods also revealed additional retinotopic features anterior to V4v. Taken together, these features indicate the presence of an additional retinotopic map, comprising a previously undifferentiated cortical area that we call 'V8'. This continues the naming scheme begun by Zeki and colleagues, who identified areas V1 through V6[12–15,21,22,34]. (We also identified an area 'V7', which is a representation of the contralateral lower visual field anterior to human V3A.)

Area V8 has a unique polar angle retinotopy and a distinctive foveal representation. This contrasts significantly with the three extrastriate representations posterior to V8 (V4v, VP, and the inferior wing of V2), all of which are quarter-field representations of the contralateral upper visual field. Although the polar-angle retinotopy in V8 includes an additional representation of this quarter field, it also extends further to include a lower-field representation as well (Figs 2 and 3). These three extrastriate visual areas (V4v, VP and inferior V2) also share a contiguous representation of the fovea, at the top (superior) end of this row of areas (Fig. 2d). However, the foveal representation in V8 is not part of this contiguous foveal band; instead it is located about 3.5 centimeters away along the cortical surface, at the anterior border of V8 (Fig. 2d).

HUMAN VERSUS MACAQUE MAPS

Because so much of the historical controversy about cortical color processing arose in studies of macaque monkey, it is natural to wonder which area in macaque corresponds to area V8 in humans. To clarify the topographic relationship of the human and macaque maps, we first averaged together

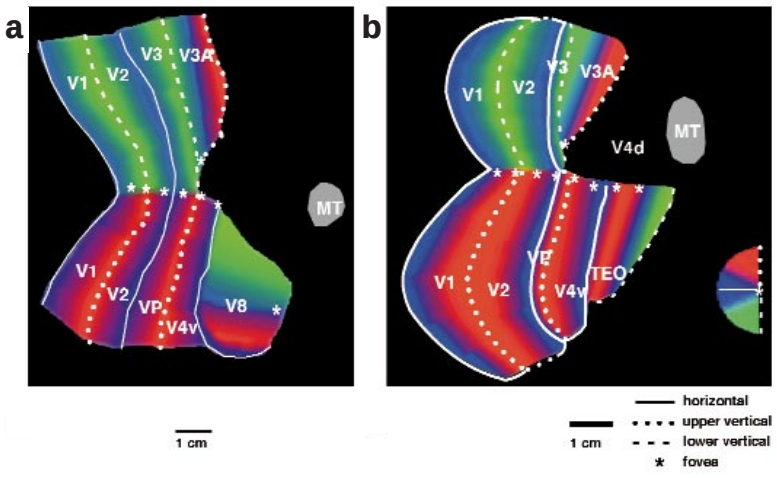

Fig. 4. Comparison of the polar angle retinotopy in human visual cortex, relative to that reported in macaque monkeys. In both species, visual cortex is shown in flattened format, with visual area boundaries and polar angle continua as in Fig. 2a–c. Area MT is shown in gray. In macaque, dorsal area V4 is also indicated (V4d). The retinotopy of V8 is similar to that reported in area TEO, in that both areas are located immediately adjacent to area V4v. However, the two areas differ in overall shape, and the retinotopy of V8 is rotated approximately 90° relative to that reported in TEO.

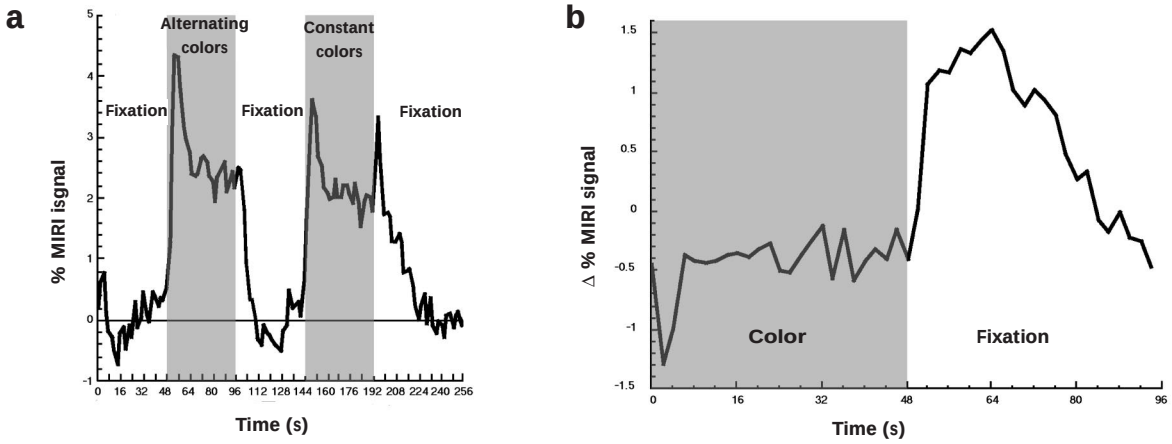

Fig. 5. The time course of V8 activity is related to the perception of color afterimages. **(a)** Time course from all voxels in retinotopically defined V8 that responded (p<0.00001) to the colored stimuli, relative to the initial presentation of the uniform gray stimulus, averaged across 16 MR scans, showing the response to both the actual and the illusory color stimuli. Epochs in which subjects viewed a uniform grey field, or an illusory afterimage on a gray background, are indicated with a white background; epochs when the subjects viewed colored stimuli (alternating- or constant-colored) are indicated with a gray background. After the color stimulus, subjects viewed a uniform gray field, or an illusory afterimage on a gray background. During a color afterimage, the fMRI response was quite prolonged, consistent with the time course of the percept of the illusory colors. **(b)** The MR afterimage is shown more directly by subtracting signal during constant color and subsequent gray period from alternating color and subsequent grey period.

six of the most robust human retinotopic maps, using digital morphing techniques (Fig. 4b) as described[26]. These averaged maps could then be compared to the map of macaque retinotopy, as estimated from single-unit mapping[35] (Fig. 4a). This comparison suggests that human area V8 shows some retinotopic and topographic similarity to macaque area TEO. Furthermore, TEO and/or more anterior areas have appeared strongly color selective in recent studies of macaque visual cortex (refs 17–19, 28, Vanduffel *et al. Soc Neurosci. Abstr.* 23, 845, 1997).

However, the retinotopic similarity between V8 and TEO is far from exact (Fig. 4). Furthermore, other investigators have proposed different area boundaries in this region of macaque cortex[36–38]. Unfortunately, those alternative models of the macaque maps are even less similar to the empirical human maps in this region of cortex. Thus it is not clear which macaque area is homologous to human area V8. However, the flat maps in Fig. 4 do make it clear that this human collateral color area is not topographically similar to macaque V4 (neither dorsal nor ventral subdivisions). Human V8 is also topographically inconsistent with the location of subdivisions proposed in macaque dorsal V4, such as V4t (ref. 39) and V4A (e.g. ref. 14).

Color afterimages

Another way to assess functional selectivity is by measuring the fMRI responses during visual aftereffects, rather than during the fMRI effects produced by the visual stimuli themselves. In other dimensions such as motion[40] and orientation[41], such indirect aftereffects have ironically proven to be functionally more selective than the effects themselves. Here we tested whether illusory color would also activate V8, as did real color stimuli.

If one stares for a time at a saturated color, then looks away at a uniform gray field, one sees an illusory percept of the complementary color. Unlike motion or orientation aftereffects, these negative color afterimages are thought to arise primarily in the retina[42,43]. However, they also presumably trigger activity at higher levels, as would a real stimulus that was similarly stabilized on the retina[29,44]. To test for the presence of fMRI responses to these illusory colors, we produced such color afterimages in the MR scanner, along with control stimuli that were very similar but did not produce color afterimages.

Figure 5 shows the time course of fMRI activity produced by these stimuli in area V8. As expected, the colored stimuli produced robust fMRI activity in V8, whether alternating or constant. However, only the constant-colored stimuli produced a perceptual color afterimage and a corresponding fMRI aftereffect in V8 during subsequent viewing of the uniform gray field (Fig. 5a). The alternating-colored stimuli produced neither a perceptual color afterimage nor a prolongation of the normal fMRI return to baseline during the subsequent viewing period (Fig. 5a). The duration of the isolated fMRI color aftereffect was prolonged, consistent with the prolonged duration of the illusory color percept (Fig. 5b). Overall, this strongly suggests that these fMRI responses were related to the processing of the illusory colors.

One unexpected finding was that the stimuli with alternating colors produced slightly more activity than the stimuli in which color remained constant (Fig. 5a). This may reflect the fact that the hues in the constant-colored stimuli become progressively less saturated (less densely colored) with time because of chromatic adaptation[45]. Essentially one begins to see the mixture of the color afterimage and the actual color, Because these two colors are complementary, they produce a less saturated, more 'washed-out' color. This decreased fMRI response to the decreasingly saturated colors supports the other evidence that V8 is involved in color perception.

Findings similar to our fMRI afterimages in V8 were reported from scattered voxels in single-slice imaging through nearby posterior fusiform gyrus[29], but the location of those voxels was not localized to any specific cortical area. However,

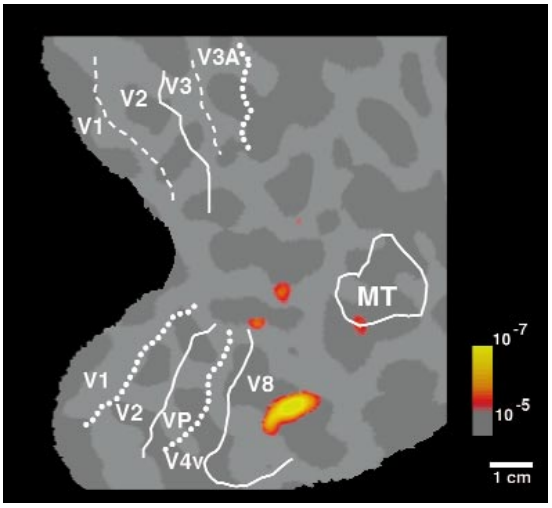

Fig. 6. The perception of color afterimages produces relatively higher activation in cortical area V8, compared with other cortical areas. The activation shown here represents all regions that responded significantly more ($p \leq 0.00001$) during viewing of the uniform gray stimulus following the constant color stimulus, compared with viewing of the same gray stimulus following the alternating color stimulus.

none of these data address the possibility that similar fMRI afterimages occur nonspecifically throughout much wider areas of visual cortex. This could arise from retinal color processing that is transmitted passively to cortex, or from globally increased attention when viewing the color afterimages.

To test this, we reanalyzed our data to find the areas in an activity map that respond differentially during the presence of the visual afterimage (Fig. 6). At lower levels of significance than shown here, a number of additional visual areas (e.g. V1, V2) do respond more to color afterimages. However, at the more strict significance threshold used in Fig. 6, the activity in V8 was more prominent than in any other area. In particular, the wider areas of foveal color selective activities including areas such as V1, V2, etc., were relatively less prominent in the afterimage test, compared to the direct comparisons of color versus luminance (see Fig. 1c and Fig. 6, showing the same hemisphere).

Discussion

The retinotopic maps make it clear that an additional area (V8) exists beyond those areas described previously in human visual cortex. Area V8 is retinotopically distinct from the previously described area V4v, based on at least four different criteria. First, V4v and V8 have separate foveal representations, approximately 3.5 cm apart along the cortical surface. Second, V4v and V8 each include separate representations of the upper visual field, separated from each other by a representation of the horizontal meridian. Third, V8 differs from V4v in its global functional properties, including but not limited to color sensitivity. Fourth, the nature of the retinotopy in V8 is different from that in V4v.

The direct comparisons between color- and luminance-varying stimuli (Fig. 1) indicate that area V8 responds slightly better than neighboring cortical regions to colored stimuli. However, we also found that the color-varying stimuli produce preferential activation in the foveal representation of all retinotopic areas. Thus, V8 may seem especially biased for color stimuli merely because its foveal representation sets it topographically apart from the conjoined foveal color responses of its neighbors (Figs 2 and 3). This is a relatively trivial explanation for the color selectivity reported earlier, but we cannot rule it out completely. This idea is further supported by the fact that area V8 responds at reasonable levels to a wider variety of visual stimuli.

However, other evidence argues that V8 is involved in wavelength-dependent processing and perhaps in the conscious perception of color itself. The robust and selective response to illusory colors (Figs 5 and 6) strongly supports this idea. Also, the anatomical colocalization of V8 compared with the previous clinical data makes it likely that area V8 is damaged in achromatopsic patients[23–25].

What do these human data tell us about macaque visual cortex? This question is constrained by several factors. The human data are based on clinical and neuroimaging data, whereas the macaque data are derived from different techniques (e.g., single units, lesions and DG imaging), which could conceivably produce different results. Also, there may be significant biological differences between the cortical organization of color sensitivity in humans compared with macaques. As we learn more about human and macaque visual cortex, the number of differences between these species are increasing correspondingly[26,46–48].

Despite these caveats, the data suggest that the area of macaque cortex that is homologous to the human 'achromatopsia' area should be located in or anterior to TEO, rather than in V4. This is supported by data from macaque[17–19] as well as the present data from human V8.

Methods

GENERAL PROCEDURES. Except for modifications described below, the methods in this study are similar to those described[26]. Informed written consent was obtained for each subject prior to the scanning session, and all procedures were approved by Massachusetts General Hospital Human Studies Protocol numbers 90–7227 and 96–7464. Normal human subjects, with (or corrected to) emmetropic vision, were scanned in General Electric magnetic resonance (MR) scanners retrofitted with ANMR echo-planar imaging. Most scans were acquired in a high-field (3 T) scanner, but some early scans were acquired in a scanner of conventional (1.5 T) field strength. Based on signal-to-noise ratios obtained during otherwise comparable conditions, four functional scans at 1.5 T were found to be approximately equal to one functional scan at 3 T, so this was the ratio used to equate data acquired from the two scanners. Head motion was minimized by using bite bars with deep, individually molded dental impressions. The subject's task in all experiments was to fixate the center of each type of visual stimulus throughout the period of scan acquisition.

MR images were acquired using a custom-built quadrature surface coil, shaped to fit the posterior portion of the head. MR slices were 3-4 mm thick, with an in-plane resolution of 3.1 x 3.1 mm, oriented approximately perpendicular to the calcarine fissure. Each scan took either 4 min 16 s (color-versus-luminance and color afterimage scans) or 8 min 32 s (retinotopy), using a TR of either two or four seconds, respectively. Each scan included 2,048 images, comprised of 128 images per slice in 16 contiguous slices.

Improved retinotopic maps were obtained from 32 subjects (79 scans polar angle, 79 scans eccentricity, 323,584 images total). Among them, 13 subjects were also tested for color-versus-luminance (112 scans, 229,376 images total). Of these, five subjects were tested extensively for color afterimages (100 scans; 204,800 images total). In most subjects, additional scans were done to clarify the location of area MT and other visual areas.

VISUAL STIMULI. The goal of the first color-related experiment (Fig. 1) was to map the MR activity produced by color- versus luminance-varying stimuli throughout visual cortex, using conventional psychophysical stimuli. Prior to scanning, the equiluminance values for different color combinations (red-cyan, CIE x and y coordinates 0.645, 0.345 and 0.185, 0.248 respectively, or green-purple, CIE x and y coordinates 0.277, 0.684 and 0.351, 0.220, respectively) were measured for each subject, outside the scanner. Equiluminance was measured using a motion-null test, with the same stimulus projector (NEC model MT 800), lens and color software used subsequently in the MR experiments. In the first experiment, both color- and luminance-varying stimuli were produced using slowly moving (0.5 Hz) sinusoidal radial gratings ('pinwheels') of low spatial frequency (3 cycles per revolution). The gratings varied either in achromatic luminance (maximum, 95% luminance contrast) or in equiluminant color (at maximum available saturations of the display device within constraints of approximately 140 cd per m^2 mean luminance and approximately white mean chromaticity), in direct alternation, in 16-second epochs, using 16 epochs per scan.

In a second experiment (Figs 5 and 6), color afterimages were produced by showing subjects colored adaptation patterns. Subjects adapted to two general types of stimuli; one produced a pronounced color afterimage when subjects subsequently viewed a uniform gray field, but a very similar control stimulus did not produce such a color afterimage. There were five epochs in each scan, presented in the following order: (1) uniform gray, (2) alternating-color (control adaptation), (3) uniform gray, (4) constant-color (experimental adaptation) and (5) uniform gray. All epochs were 48-s long, except that the final fixation period was prolonged 16 s to reveal the final traces of the MR afterimage. In the analysis for Fig. 5b, the last 16 s in that final epoch was truncated to match the duration of all other epochs. Both the constant- and the alternating-colored patterns were comprised of complementary colors (red-cyan or green-purple), spatially arranged in opposed quarter-fields (i.e. two-cycle-per-revolution polar square waves), akin to interleaved bow ties. All hues were presented at equal luminance, based on motion-null tests in each subject. Following adaptation to the constant colors, subjects initially experienced a prominent color afterimage against the uniform gray background, which faded over tens of seconds. The afterimage was retinotopically similar to the adaptation stimulus, but of complementary color. As controls, we presented stimuli equivalent to the constant colors, except that the colors alternated between color and complementary color, reversing every 2 s. The latter condition produced no perceptual color afterimages during the subsequent epoch of uniform gray stimulation.

Stimuli for retinotopic mapping were slowly moving, phase-encoded thin rays or rings comprised of counterphasing black and white checks, scaled according to polar coordinates, similar to those described[26,31,32,50]. However, to produce the most informative retinotopic maps possible, several stimulus modifications and new procedures were implemented. First, all retinotopic measurements were made in the 3 T scanner. This increased the MR amplitudes by a factor near four, and the physiological signal-to-noise ratio by a factor near two. Second, we signal-averaged the information from 4–12 scans (8,192–24,576 MR images) of polar angle or eccentricity. Data were also combined from different slice prescriptions on the same cortical surface, to reduce intervoxel aliasing. Third, the retinotopic stimuli were increased in extent both foveally and peripherally, to extend from 0.2° through 18–30°. This activated correspondingly more surface in each cortical area. Fourth, the visual stimuli were presented using a new LCD projector of higher spatial resolution (800 x 600), using better optics than previously (aperture lens, bypassing shielding screen, etc.). Fifth, the retinotopic stimuli varied in color as well as luminance, to better activate any color-selective cells in the region. The sum of all these manipulations produced very robust retinotopic maps.

DATA ANALYSIS. Data from two-condition experiments (e.g., color-versus-luminance comparisons) and phase-encoded retinotopic experiments were initially analyzed by doing a fast Fourier transform on the MR time course from each voxel. Statistical significance was calculated by converting the Fourier magnitude of the response to an f-statistic. The phase of the signal at the stimulus frequency was used to track stimulus location in the case of retinotopic stimuli, and to distinguish between positive- or negative-going MR fluctuations in the case of two-condition stimulus comparisons.

Scans comparing more than two stimuli (e.g., the color afterimage data) were analyzed by selective averaging of two conditions. This was followed by statistical comparison using a *t*-test of the difference of the first seconds following onset of the next epoch (here stimulus offset).

For topographic clarity, all data were analyzed and displayed in cortical surface format, as described[36,43,44]. This made it possible to extract the MR time courses from voxels in specific cortical areas, which were defined in the same subjects. The specific areas sampled were V1, V2, V3/VP, V3A, V4v, MT+, and V8. Area 'MT+' was defined on the basis of additional scans comparing moving and stationary stimuli[26,40]. All other areas were based on retinotopic criteria.

For ease of comparison, all hemispheres are shown in right hemisphere format. Above a minimum threshold, the statistical significance of the displayed pseudocolor range has been normalized according to the overall sensitivity of each subject, as described elsewhere.

Acknowledgments

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With color in mind

Charles Heywood and Alan Cowey

Which human brain area produces color blindness when damaged? High-resolution functional neuroimaging suggests that it is area V8, not the favorite candidate V4.

Dorothy's whirlwind departure from a monochrome Kansas into the vividly chromatic world of Oz, in the 1939 classic film *The Wizard of Oz*, highlights the substantial contribution that color makes to our visual world. Yet equally revealing is the ease with which we view monochrome film or television, where the absence of color does not compromise our enjoyment and can pass unnoticed. This is not so in the clinical condition of cerebral achromatopsia where patients, following characteristically ventral occipitotemporal brain damage (see Fig. 1a) inhabit a drab world, devoid of color, and may be painfully aware of their complete loss of chromatic vision[1]. Attempts at understanding the nature of cerebral achromatopsia and its neural basis have spawned controversy ever since Louis Verrey's description[2] of such a case in 1888 (see ref. 3 for review). The ensuing debate lasted for more than a century, and not surprisingly the protagonists reflected opposing views about whether any cognitive or perceptual function was regionally localized. At issue was whether achromatopsia results from the deletion of a cortical region specialized for the processing of color. The demonstration[4], using positron emission tomography, of increased cerebral blood flow in an area of cortex when observers view chromatic scenes was certainly consistent with this notion, because the activated region, dubbed the human color center, is invariably damaged in cases of cortical color blindness. By then, however, the cluster of 20–30 visual areas occupying almost half of the neocortex of monkeys had been identified, and the debate turned to whether the human color center was homologous to the fourth visual area of the monkey, cortical area V4 (see Fig. 1b). This correspondence had been proposed chiefly on the (not uncontested) view that V4 contains a comparatively high proportion of cells that respond selectively to wavelength and color[5]. The results of a functional imaging study by Hadjikhani and colleagues, reported in this issue of *Nature Neuroscience* (pp 235–241), suggest however that the human color center is distinct from area V4. The newlydefined color area contains a complete retinotopic map of the contralateral visual half field, responds more robustly to color than neighboring regions and, unlike V4, is activated by the induction of color aftereffects. The fMRI signal elicited by an aftereffect thus mimics the response to a real colored stimulus, providing supporting evidence that V8 is implicated in processes involved in perceiving color. These properties, the authors suggest, make it a ready candidate for a region responsible for our conscious perception of a colored world.

Hadjikhani and colleagues used existing, but improved, techniques of functional neuroimaging to reveal, with increased senstivity, brain areas involved in the processing of color. Functional magnetic resonance imaging (fMRI) relies on endogenous changes in magnetic susceptibility, which result from changes in local cerebral blood flow and oxygenation. Such changes are activity dependent, and their measurement in response to visually presented stimuli have already established the borders of a number of visual areas in the human brain[6]. These areas are the presumed homologues of those identified in the monkey brain using a variety of invasive techniques, such as cellular recording and experimental neuroanatomy. Delineation of an area relies on the presence of an orderly retinotopic map

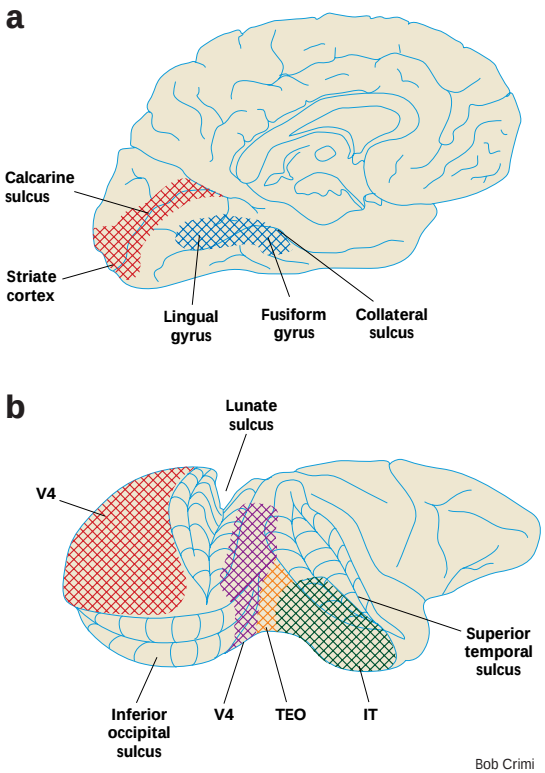

Fig. 1. Visual areas in the human and monkey brains. **(a)** The medial view of the left hemisphere of the human brain. Striate cortex, area V1, is shown in red, partly buried in the calcarine sulcus. The region along the collateral sulcus, whose destruction leads to cerebral achromatopsia, is shown in blue. Area V8 lies in the middle of the collateral sulcus, whereas V4 lies slightly more posterior and medial. The damage indicated by blue would therefore include V4v and V8. **(b)** A lateral schematic view of the right hemisphere of the macaque monkey, in which the labeled sulci have been opened up. Areas V1 (red) and V4 (purple) extend onto the ventral and medial surfaces, respectively. Areas in the temporal lobe (TEO, orange and IT, dark green), have been implicated in color vision of the macaque monkey, and Hadjikhani and colleagues raise the possibility that TEO may correspond to human V8.

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of the visual world, which is a feature of many visual areas. The authors have exploited the fMRI technique to identify such maps, using stimuli consisting of slow-moving patterns of luminance modulation. As the light and dark areas pass across the visual field, they elicit periodic excitation at the associated cortical location. Moreover, the phase of the response specifies the polar angle or eccentricity, for rotation or radial movement around the fixation point respectively, of the visual field region represented at that location. Thus a Fourier analysis on the response profile of a single voxel of the image, along with a consideration of the sign of the response to identify mirror- versus non-mirror-image representations, will yield the retinotopy of a visual area, which can displayed, by cortical flattening, as a two-dimensional map. Using such techniques, Hadjikhani and colleagues compared the effect of luminance-defined visual patterns with that of identical patterns that were defined by equiluminant color variation, that is, variations in color but not in luminance. In addition to finding stronger activation to color than to luminance in cortical areas V1, V2, V3/VP and the ventral subdivision of V4 (V4v), a region in the middle of the collateral sulcus was identified that responded preferentially and especially effectively to color. Its location corresponded to that previously (and in the absence of identification of retinotopic boundaries, prematurely) described as 'human V4'. By adopting improved techniques, including a high-field scanner, signal averaging and improved visual displays, the authors established that the true color center lies beyond the anterior border of the previously reported area V4v (i.e. outside v4 altogether). Furthermore the retinotopy of the color center differs from its neighbors. Areas V4v, VP and inferior V2 contain quarter-field representations of the upper visual field and share a contiguous representation of the fovea. In contrast, the color area contains a map of the upper and lower half-fields with a foveal representation located at its anterior border. It now seems clear that the color center is distinct from area V4, and accordingly, the authors refer to this new, previously unreported region as area V8.

Area V8 poses as many new questions as its identification sought to resolve. That it is distinct from area V4 is certainly consistent with hitherto puzzling demonstrations that ablation of V4 in the macaque monkey does not result in the severe deficits in the discrimination of hue that is the hallmark of cerebral achromatopsia[7]. Conversely, impairments in the discrimination of visually present form and pattern vision that invariably follow damage to V4 in the monkey are not an invariable feature of the vision of achromatopsic people. The location of V8 within the region destroyed in achromatopsic patients, although the latter is always more extensive and includes white matter damage, is strong but not conclusive evidence that V8 is the critical area whose removal can result in the complete loss of the conscious representation of color. As Hadjikhani and colleagues themselves point out, the question naturally arises as to where area V8 is concealed in the macaque monkey's brain. Localization of macaque V8 would lead to confirmatory evidence that its removal results in cortical color blindness. They speculate that area TEO[8,9] (Fig. 1b), a region lying anterior to V4, may be the culprit. Indeed this region, along with more anterior temporal lobe areas (Fig. 1b), has been implicated in color vision (Vanduffel, W. *et al.*, *Soc. Neurosci. Abstr*. 23, 334.7, 1997; Katsuyama, N. *et al.*, *Soc. Neurosci. Abstr*. 23, 803.11, 1997). Large lesions to anterior and inferior portions of the temporal lobe do render monkeys achromatopsic[10], and a high proportion of color-selective cells, revealed by metabolic labeling and electrophysiological recording, reside in this area[11].

Although the precise role of area V8 has yet to be clarified, determining what is spared, as opposed to lost, in cerebral achromatopsia may provide some signposts. Color makes a ubiquitous contribution to vision. Color differences can, among other things, provide information about form, texture and motion. This is presumably reflected in the number, and wide variation, of activated areas reported in neuroimaging studies when subjects perform a wide variety of color-related tasks. Cerebral blood flow can be modulated by the nature and difficulty of the behavioral tasks (whether they entail passive viewing, active discrimination or directed attention) and the properties of the visual display (containing equiluminant color, with or without form, with or without associated brightness differences). The physical basis of color is the wavelength composition of light. Many cortical areas prior to V8 contain cells that are sensitive to, but not selective for, wavelength differences. For example, cells may respond vigorously to equiluminant red/green borders without signaling the nature of the colors of which the border is composed, i.e. which is red and which is green. Form can thus be derived from the processing of wavelength differences and yield information about the visual scene without encoding its chromatic content. It should perhaps come as no surprise that achromatopsic patients, lacking area V8, can show a preserved capacity to use wavelength variation to detect motion and form[12], presumably mediated by earlier and intact extrastriate areas. Detection of equiluminant chromatic form can even be achieved when it is disguised by accompanying rapid random luminance variation. The latter implies that patients must retain color-opponent processing mediated by the well known P-channel of primate vision, which unlike its partner the M-channel is blind to the introduction of rapid flicker. Moreover, another paper in this issue[13] reports that profoundly achromatopsic patients lacking evidence for residual color-opponent processes are still able to extract motion from high-contrast color cues.

Achromatopsic patients can therefore process wavelength differences to extract information about form and motion, but their brain damage nevertheless renders them blind to color differences. Such brain damage is, of course, likely to encroach on territory other than area V8, including the adjacent V4v. Although loss of conscious representation of hue characterises achromatopsia, another very different explanation has been offered[3], namely that it is a failure of color constancy—a loss of the invariance of an object's perceived color despite wide variation in the wavelength composition of the illuminating light. Although it has been suggested that the chromatic responses of neurons in area V4 show color constancy[14], the effects of ablating this in the monkey have yet to convincingly demonstrate a corresponding deficit. Might V8 be assigned such a role? An explanation of cerebral achromatopsia as resulting from the destruction of V8 with a concomitant deficit in color constancy does not readily explain why two very different equiluminant hues are indistinguishable to an achromatopsic patient, nor why the world should be described in shades of gray. A direct test of color constancy in one such patient does not lend unequivocal support for this view[15]. When two patches of different spectral composition were presented against two different backgounds, one to each eye, the

patient reported them to be indistinguishable only when the ratios of the retinal cone response of path/background were preserved. When the ratios were different for each eye, the patches no longer appeared identical. These responses are akin to those of the normal observer and are presumed to be mediated by retinal mechanisms. However, the achromatopsic patient departed from normal performance when presented with more complex scenes requiring multiple cone contrast comparisons. Achromatopsic patients may therefore retain rudimentary color constancy mechanisms, and it remains an open question as to whether V8 is essential for consolidation of information across large regions of complex scenes.

However, what these patients do lack is the conscious representation of color. If it transpires that a single cortical area, area V8, is indispensable for our conscious percept of color, it will indeed be a rare triumph for the view that regional specialization underlies the cluster of visual areas that occupy a substantial proportion of the neocortex in primates. On a note of caution, however, Hadjikhani and colleagues hint that area V8 responds to a wide variety of visual stimuli. The challenge will then be to establish the precise role of this, and other areas, in the cortical processing of color. Hadjikhani and colleagues have pointed us in the correct direction.

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Zinc, Src and NMDA receptors—a transmembrane connection

Philippe Ascher

Zinc and tyrosine kinases produce opposite effects on the NMDA receptor; new evidence suggests that Src-induced potentiation is due to the relief of zinc inhibition.

Recently, scientists have become increasingly aware of the potent actions of zinc and tyrosine kinases on NMDA receptors. NMDA receptors are a group of ionotropic glutamate receptors that are permeable to both calcium and sodium, and have been implicated in many forms of synaptic transmission, synaptic plasticity and in cell death. Zinc had long been known to interact with many neurotransmitter receptors, but its inhibition of NMDA receptors has attracted particular interest because of a possible functional role. Zinc is stored in synaptic vesicles in a number of glutamatergic terminals of the forebrain, is released during synaptic activity, and its concentration in the synaptic cleft has been suggested to rise to the micromolar range[1]. Early studies of the interaction of zinc with NMDA receptors[2,3] identified two effects, a voltage-dependent inhibition which resembles that of magnesium, and a voltage-independent inhibition, which occurs at a different site. The two effects were initially described for zinc concentrations in the micromolar range, and this fitted nicely with estimates of zinc concentration in the synaptic cleft following glutamate release. Recently, after the cloning of NMDA receptors subunits allowed the expression of recombinant receptors, the two effects of zinc were further analyzed using NMDA receptor subtypes built from specific combinations of subunits. Using these recombinant receptors, additional evidence was obtained to support the hypothesis that the voltage-dependent effect of zinc occurs via the same site as the voltage-dependent magnesium block within the channel pore, but that zinc permeates the channel better[4]. The binding site involved in the voltage independent block is less well identified, but in some recombinant NMDA receptors (those assembled from NR1 and NR2A subunits) the IC_{50} of the voltage-independent inhibition is exceptionally low (10 nM-100nM) [4-6]. This is the range of concentration at which zinc is present as a 'contaminant' in most experimental solutions, but also in the cerebrospinal fluid. Thus, even without adding any additional zinc, a large fraction of the high-affinity, voltage-independent, inhibitory sites on NR1-NR2A receptors are already occupied, so that the addition of a zinc-chelating agent to the bath is usually sufficient to double the amplitude of the baseline response[4].

The interaction of tyrosine kinases with NMDA receptors *a priori* seemed to have little relation with that of zinc. The early observations of Salter and colleagues[7,8] showed that tyrosine kinase inhibitors inhibit some NMDA responses, which conversely can be potentiated by intracellular injection of either a constitutively-active form of the intracellular tyrosine kinase Src or peptide fragments that activate Src[8]. Similar effects were observed with another tyrosine kinase, fyn[9]. These observations were reinforced by reports that tyrosine kinase inhibitors interfere with some forms of long-term potentiation (a cellular model for learning and memory), and that some tyrosine kinase deficient mice had perturbed LTP and behavioral abnormalities (for references see 10). Once again, recombinant NMDA receptors were used to reveal a subunit specificity: Src only acted on receptors assembled from NR2A subunits and a restricted group of splice variants of NR1[9].

Zheng and colleagues on page 185 of this issue of *Nature Neuroscience*[11] have linked these two sets of apparently independent observations by experiments that strongly suggest that the potentiating effect of Src on NR1-NR2A receptors results from the suppression of the ambi-

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Has a new color area been discovered?

TO THE EDITOR – A recent paper in *Nature Neuroscience*[1] claims to show "a previously undifferentiated cortical area that we call V8" in the human fusiform gyrus. This claim has given hopes to some[2] that the cortical area responsible for the conscious perception of colors in humans has at last been found. However, the Talairach coordinates for this 'new' area "V8" (ref. 1) are identical to those that we had published for V4 (ref. 3). The authors have therefore not found a new area; instead they have rediscovered and tried to rename area V4. Furthermore, their report[1] states, in reference to our paper[3], that "a prior study also concluded that this human color-selective region included a representation of upper and lower visual fields". How, then, can they state that colors activate "area V8 but not V4" (ref. 1)?

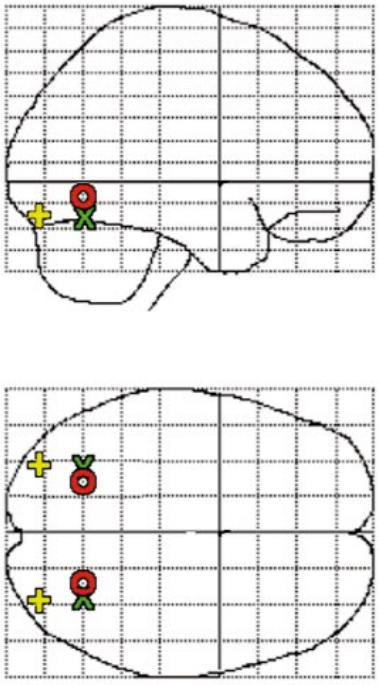

Fig. 1. The figure shows the locations of the three areas that are discussed in the text, in a glass brain projection. The areas were located by using the Talairach coordinates of the three areas given in the paper by Hadjikhani *et al.* (1998): O corresponds to area V4 defined in Lueck *et al. Nature* **340**, 386–389 (1989); Zeki *et al. J. Neurosci.* **11**, 641–649 (1991); McKeefry and Zeki *Brain* **120**, 2229–2242 (1997). X corresponds to the 'new' area 'V8' of Hadjikhani *et al.* and the + to the area V4v defined by Sereno, M.I., *et al. Science* **268**, 889–893 (1995).

The answer is simple: it hinges on the use of the letter v, enabling one to write of V4 or V4v. To understand how a single letter can lead to such confusion, one has to retrace the history of the subject briefly. In 1995, Sereno and his colleagues, including Roger Tootell, co-author of ref. 1, reported the results of their mapping experiments in human visual cortex[4]. Many of the areas described had maps similar to ones found earlier in the macaque. Their map of what they supposed to be human V4 was not so straightforward. They distinguished a ventral V4v, located in the fusiform gyrus, from a dorsal V4d, located dorsolaterally, the two separated from each other by a relatively large expanse of cortex. V4v was clearly shown in the diagrams, but not V4d. This separation was unlike the V4 map in the monkey, where the two subdivisions, representing lower and upper visual fields respectively, are continuous with each other[5].

This made us suspicious, because the clinical evidence shows that lesions in the fusiform gyrus, where we had located V4 (refs 3, 6) can result in total hemi-achromatopsias[7,8] that include both upper and lower quadrants of the visual hemifield. We therefore undertook a mapping experiment[3] and found, unlike the Sereno report[4], that both quadrants are mapped within the color center (area V4) in the fusiform gyrus of each hemisphere. Human V4, like monkey V4, therefore contains a complete map of the visual hemifield in each hemisphere. It is this crucial finding that Hadjikhani *et al.*[1] have now confirmed. Not surprisingly, the Talairach coordinates of their 'new' area are identical to those of V4 (±26, -67, -9 for our V4 and ±33, -65, -14 for the 'new' color area) but differ significantly from the coordinates of the more posterior V4v, at ±32, -87, -16 (Fig. 1).

Now we can see how one can write that color selectivity "is located in area V8, rather than in 'V4'" (ref. 1) or pretend that cerebral achromatopsia is produced by lesions of "area V8, not the favorite candidate V4" (ref. 2). One can do so by simply dropping the v from the V4v and not stating explicitly that the human color center is distinct from V4v, though identical in position to V4 (refs 3, 6). Both the above quotes would be correct, if the v were reinstated into the V4; both are wrong without it, as is the statement that "the human color center is distinct from area V4" (ref. 1). Whether this attempted renaming solves any of the mysteries of conscious color perception remains to be seen.

By stating that "color-selective activity is located in area V8 rather than in 'V4'" (without adding the v), they have misled readers into believing that they have identified a new color area[2]. That is the central issue that the authors ought now to address unambiguously, by acknowledging that they have not discovered a previously undescribed area, that color activates V4 selectively but not V4v, and that the coordinates of the human color center coincide with what we have given for V4 (refs 3, 6) but differs from that of their V4v. We leave it to them to describe in another context their area V4v, which is the area that seems to have no monkey equivalent and thus represents the real new discovery.

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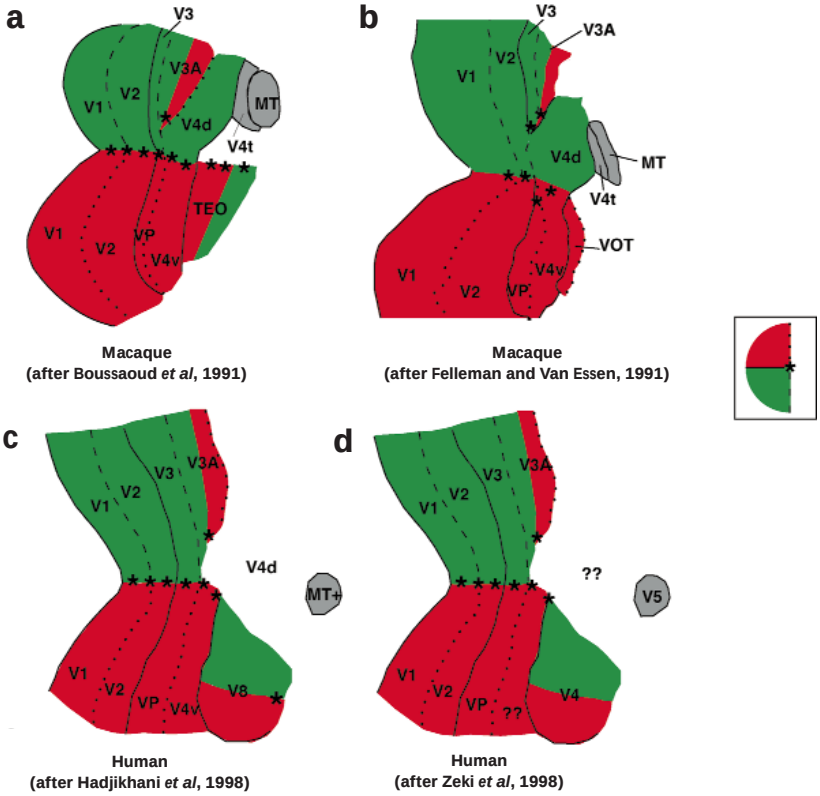
TOOTELL AND HADJIKHANI REPLY – Macaque V4 is a cortical visual area that is often subdivided into dorsal and ventral parts ('V4d' and 'V4v'), comprising the retinotopic representations of the lower and upper visual fields, respectively. This has been reported in numerous articles and is not in dispute. Nevertheless, Zeki and colleagues make the following claims: (1) human area V4v "seems to have no monkey equivalent, and thus [it] represents the real new discovery," and (2) our human area V8 is actually equivalent to macaque V4. Their claim is based on three properties that they require of human V4: (3) human V4 should include a representation of both upper and lower visual fields, (4) human V4 should be color-selective and (5) human V4 coincides with the neural region affected in clinical achromatopsia.

Our response to each of their five points follows. (1) Human V4v is not a newly discovered area, as claimed by



Comparison of visual cortical maps in Old World primates, drawn by different authors. All maps were drawn from right hemispheres in flattened cortical format, to approximately the same scale. (**a**) and (**b**) were based on electrophysiological and connection evidence from macaque monkeys. (**c**) is based on the retintopic fMRI maps from five human hemispheres, digitally averaged (see Hadjikhani *et al*., 1998). (**d**) is the revision suggested by Zeti *et al*.,1998, as we understand it.

Zeki *et al*. Retinotopically and topographically, human V4v is entirely equivalent to macaque V4v (for example, refs 5, 9, 10; compare Fig. 2c to a and b). V4v is not even novel in humans, since it was defined equivalently by us[4,11] and by others[12] prior to Hadjikhani *et al.*[1].

(2) Almost all work from macaque V4 (including Zeki's reports of color selectivity) has been based on recordings from the dorsal subdivision of V4, 'V4d'. Can the human equivalent of macaque V4d be the area involved in human achromatopsia (in the collateral sulcus/fusiform gyrus)? All aspects of the human cortical map (including the topography of V4v) confirm that any human homologue of V4d would be located superior to V4v, and between V3A and MT, exactly as in macaques (Fig. 2a–c). Thus, V4d should be even farther from the human color area than V4v. Retinotopic maps taken from human V4d have not been published yet, but the macaque maps would predict a lower visual field representation there.

(3) We agree with Dr. Zeki that any human 'V4' should represent the complete contralateral visual field, including both upper and lower visual fields. However, all visual areas are expected to have this property, so this argument does not help us find human 'V4'.

(4) Unlike Dr. Zeki, we had no preconceptions that retinotopically defined human V4 would also show high color selectivity. After much research and controversy[2,13], macaque V4 (or any subdivision thereof) does not seem unusually color selective. For instance, after Zeki's initial report claiming that 100% of the cells in V4 were color selective[14], the percentage of reported color-selective cells shrank over the succeeding years, under increasingly detailed scrutiny (87% in 1977, ref. 15; 68% in 1978, ref. 16; 32% in 1978, ref. 17; 20% in 1981, ref. 18; 10% in 1981, ref. 19; and 18% in 1982, ref. 13). If one does not presume that human V4 is necessarily color selective, it is easier to evaluate the human retinotopy on its own merits. If one is instead convinced that human V4 must be color-selective, the complicated rearrangement in Fig. 2d may be the best fit one can make to the actual evidence.

(5) Hadjikhani *et al.*[1] confirm the reports of Dr. Zeki and colleagues of color selectivity in a region implicated in achromatopsia (in the collateral sulcus/fusiform gyrus). However, our analysis indicates that this color-selective area is not equivalent to macaque V4, which is why this area required a new name (V8).

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