The clinical and functional measurement of cortical (in)activity in the visual brain, with special reference to the two subdivisions (V4 and V4α) of the human colour centre

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ABSTRACT

We argue below that, at least in studying the visual brain, the old and simple methods of detailed clinical assessment and perimetric measurement still yield important insights into the organization of the visual brain as a whole, as well as the organisation of the individual areas within it. To demonstrate our point, we rely especially on the motion and colour systems, emphasizing in particular how clinical observations predicted an important feature of the organization of the colour centre in the human brain. Using functional magnetic resonance imaging (fMRI) data analysed by statistical parametric mapping (SPM) and independent component analysis (ICA), we show that the colour centre is composed of two subdivisions, V4 and V4α, the two together constituting the V4-complex of the human brain. These two subdivisions are intimately linked anatomically and act cooperatively. The new evidence about the architecture of the colour centre may help to account for why the syndrome produced by lesions in it, that of cerebral achromatopsia, is so variable.

Keywords: achromatopsia, colour vision, perimetry, independent component analysis (ICA).

1. INTRODUCTION

The present confidence and euphoria in charting the involvement of different parts of the human brain in different and distinct activities is well justified. Never before in human history have we been able to explore with such assurance activities which, like language, are distinctly human, or begin to probe with such hope what has commonly been regarded as subjective mental states such as emotion. Yet whatever bright promise the methods of functional imaging might hold for the future, the measurement of brain activity or inactivity must ultimately rely on other disciplines as well. In this article we emphasise one other discipline, clinical observation, and show that this relatively crude and time-honoured method can still contribute in significant ways to detecting and unravelling, and even measuring, cortical activity in ways not less important and informative than the relatively sophisticated techniques of functional imaging alone. We choose vision, and especially colour vision, as a vehicle for this view, but there is little doubt that other functions could serve as well..

2. MEASURING CORTICAL (IN)ACTIVITY THROUGH PERIMETRY

The method of visual perimetry i.e. the method of determining blind parts of the field of view has been one of the most outstanding in charting damage to the visual brain and therefore measuring indirectly those parts of the brain that are inactive. It is not often remembered that Henschen and his successors in Japan and England (Henschen 1893, Inouye 1909, Holmes 1918) had charted with considerable accuracy the representation of the visual field in the primary visual cortex, area V1 (calcarine cortex in humans), long before physiologists did so with their more sophisticated invasive techniques in monkeys (Daniel and Whitteridge 1961). The detection of a congruous scotoma, or a blind part of the

field of view at the same location for the two eyes, is a sure way of localising a lesion to the postgeniculate level, i.e. probably to areas V1 or V2 of the cerebral cortex. One can make a fairly good guess as to whether it is on the upper or lower bank of the calcarine sulcus and how far antero-posteriorly it is located by noting the position of the scotoma in the field of view. The details of this procedure, and the reliability with which the damage can be located, are so well documented that we need not dwell on it in any detail here, save to say that the method continues to provide new and interesting information about the organisation of other visual areas. For example, Horton and Hoyt (1991) have used the perimetric method to show how a well circumscribed lower quadrantanopia in patients can be used to explain the nature of visual field representation within two visual areas, V2 and V3, of human occipital cortex. The special feature of the two patients they examined was that, in both, the lesions were outside the calcarine cortex and had produced quadrantanopias with a sharp cut-off at the horizontal meridian. Relying on the known retinotopic organisation of areas V2 and V3 in the macaque monkey (Cragg 1969, Zeki 1969), they have argued convincingly that, because the upper and lower quadrants in V2 and V3 are separate and because the horizontal meridian forms the boundary between the two, it follows that a scotoma whose characteristic is a quadrant with a cut-off at the horizontal meridian must be due to a lesion of V2 and V3 rather than V1. Apart from the use to which such perimetry was put to give insights into the manner in which the retina is mapped in these two areas, this work is additionally important in showing that lesions confined at least to area V2, and possibly V3, also result in scotomas. Interestingly, despite the completely intact visual pathways up to and including area V1, these patients did not have conscious percepts of the kind of stimulus thought to be processed by V1 within their scotomas. This suggests that activity in V1 alone is not sufficient to create a conscious percept, consistent with what has been proposed on other grounds (Crick and Koch 1995). We suggest here that lesions in a certain area will only lead to visual defects for the attribute and for the level of processing that area is specialised for (Bartels and Zeki 1998). If the organization of human visual cortex is similar to that of monkey, then it is likely that lesions in V2 will cause scotomas involving the perception of edges, local motion and wavelengths, which are all processed in V2 (Hubel and Livingstone 1987, DeYoe and Van Essen 1988, Zeki and Shipp 1988); however, global motion is likely to be still perceived even within the scotoma since the motion area (V5) does not entirely rely on input from V2 (see below). By contrast, V3 is more specialized, at least in the monkey (Zeki 1978), and hence lesions in it are less likely to cause global scotomas or hemianopias.

The above are examples in which perimetry is, in a sense, measuring inactivity in the cortex, or rather detecting damaged and therefore inactive areas. But perimetry has also been instrumental in detecting active areas of the brain. For example, using dynamic perimetry, Riddoch (1917) had shown that patients blinded by lesions in area V1 could nevertheless detect motion, consciously, in their field of view. He provided a somewhat doubtful explanation for this, supposing that it was due to the sparing of those parts of V1 that are specialised for the detection of motion, which is why Sir Gordon Holmes found it so easy to dismiss Riddoch's findings: it seemed improbable that gunshot wounds would selectively spare motion-detecting cells whose distribution in V1 was in any case unknown at that time (see Zeki 1991 for a review). Although it is perhaps unwise to give too much credit retrospectively for findings whose true significance was not so explicitly recognised by their authors, it is worth recording that, in spite of this improbable explanation, the contribution that Riddoch made through his relatively crude methods of detection is writ large in the title of his paper: "Dissociations of visual perceptions due to occipital injuries", a concept that was only to be taken seriously over 70 years later, once anatomical and electrophysiological evidence had established the presence of separate systems dedicated to processing different attributes of the visual world. In addition, Riddoch was led by his simple methods to conclude that "Movement may be recognized as a special visual perception" (Riddoch 1917) - an insight ignored by the neurological world until the discovery of visual areas specialized for processing visual motion (for a review, see Zeki 1991). But Riddoch's simple methods and accurate observations resulted in more that is of topical importance for imaging studies. His 'blind' patients, he wrote, were "conscious" of having seen the motion within their blind fields, a term he repeatedly used in describing the results of his perimetric studies, almost certainly without realising the true significance of his description. It was to take physiological and imaging experiments some 75 years to find a valid anatomical and physiological explanation for this phenomenon of conscious vision for motion, in subjects blinded by lesions to V1. This was done by showing that the cells of area V5 in the macaque maintain their directional selectivity to motion when disconnected from V1 (Rodman *et al.* 1989, Girard *et al.* 1992); that, in humans, signals from fast moving stimuli reach area V5 before they reach V1 (Beckers and Zeki 1995, ffytche *et al.* 1995); and that there is significant activity in V5, without parallel activity in V1, when blind (hemianopic) patients experience consciously fast motion in their "blind" field (Zeki and ffytche 1998). It is somewhat unfortunate that Riddoch's observations disappeared, quite literally, from the medical literature for

at least half a century (see Zeki 1993b for a review). For Riddoch was, in a sense, detecting and measuring physiological activity in the brain long before modern sophisticated techniques were able to demonstrate it; indeed there is no insight that has been derived from modern imaging techniques that could be considered to be intellectually equivalent to Riddoch's insight, had his findings been accepted. The general point that we are making here is that the simple techniques of clinical observation, and perimetry in particular, are valid and important tools for measuring cortical activity.

3. THE DETECTION OF CORTICAL ACTIVITY IN COLOUR VISION

Acquired cerebral achromatopsia provides an even more compelling reason for a serious reliance on the old techniques of perimetry and clinical observation in general. Cerebral achromatopsia is a syndrome in which, following cortical damage to a specific part of the human brain, namely the colour centre in the fusiform gyrus (see below), the patient is unable to see the world in colour but only in "dirty" shades of grey. The damage causing the syndrome was first located with relative precision by Verrey, in an article interestingly entitled "Hémi-achromatopsie droite absolue" and confirmed 11 years later by MacKay and Dunlop. Both articles, like that of Riddoch, were dismissed and relegated to oblivion for many years (for a review, see Zeki 1990). But the use of the term "hemiachromatopsia", derived from clinical observation alone, should have given powerful hints about the organisation of the visual brain, and of the colour centre in particular, which at least some of the more recent sophisticated imaging studies have ignored at their peril. It is not clear that Verrey himself understood the real significance of the term, or indeed of his more general finding (see Zeki 1993a). His discovery indicated to him that the primary visual receptive centre (the "cortical retina" of Henschen which we now call V1) was much larger than that envisaged by Henschen and Holmes and was not confined to striate cortex but included the cortex of the lingual and fusiform gyri. This supposition, which turns out to be inaccurate, is one reason among others why his findings were dismissed, especially by Henschen who wrote, apparently with some irritation, "The two cases of achromatopsia published by Verrier and Machay [*sic*] do not demonstrate, in my opinion, what these authors wanted to demonstrate" (Henschen 1893).

4. WHAT THE CLINICAL HEMIACHROMATOPSIA REVEALS ABOUT THE ORGANISATION OF THE HUMAN COLOUR CENTRE

In fact, it was left to other clinicians to understand the real significance of the term hemiachromatopsia, long before the scientists got around to measuring the cortical activity produced by viewing colours. In 1980, Damasio and his colleagues wrote: "... one single area in each hemisphere controls color processing for the *entire* hemifield. This is so regardless of the fact that such an area is "eccentrically" located, in the lower visual association cortex, classically related to *upper quadrant* processing only... The classic concept of concentrically organised visual association cortex no longer appears tenable" (Damasio *et al.* 1980, original emphasis). The conclusion derived from clinical detection and measurement seemed compelling and final. There was little reason to doubt it, especially since physiological evidence had shown that, in the monkey, an eccentrically located visual area situated in upper occipital cortex, area V3A, has a representation of both upper and lower fields within it (Van Essen and Zeki 1978). Thus our early colour imaging studies (Lueck *et al.* 1989, Zeki *et al.* 1991) paid scant attention to the problem of quadrantic representation; instead, they tried to detect the cerebral activity produced by viewing full-field multi-coloured Mondrian stimuli compared to viewing the same scenes achromatically. Our results located the colour centre to a single region, which we called area V4, in the posterior part of the fusiform gyrus.

Were our relatively simple visual stimuli the best ones to use? And was our method, of detecting blood flow changes in the cerebral cortex by the technique of positron emission tomography (PET) or blood oxygen level dependent (BOLD) changes detected by functional magnetic resonance imaging (fMRI), the best way of measuring cortical activity in response to our stimuli? An apparently remarkable technique, that of phase-encoded retinal stimulation, developed by Engel and his colleagues (Engel *et al.* 1994), suggested an alternative way. Here the response phases of individual voxels in the visual cortex are related to the position of a rotating wedge or expanding ring stimulus. Put simply, that part of the visual field which is mapped in a given brain region is given by the retinal location of the stimulating wedge at the time of the region's maximal response, taking into account the time delay of the response. A reversal in response phase is of particular interest as it marks the transition from one retinotopic map to another. This method is therefore really based strictly on detecting the retinotopic organisation of the visual areas. Its use, linked to an analysis of BOLD signals revealed an area

which was named "V4v" (Sereno *et al.* 1995, DeYoe *et al.* 1996). The use of the term "V4v" implied a similarity between it and area V4, a similarity emphasized by one of the above studies which, referring to our studies, reported that "The location of V4v corresponds to some of the locations identified in positron emission tomography studies as having color selective responses" (DeYoe *et al.* 1996); the addition of "v" was intended to indicate that it was nevertheless only the isolated ventral part of a much larger V4, in which the upper quadrant alone is mapped, which had been charted (the dorsal part, representing the lower quadrant, and thought to be located dorso-laterally in the occipital cortex, has yet to be charted (Tootell *et al.* 1996). This itself is cause for concern because it is difficult to imagine why the same method of stimulation and analysis can chart one half of an area but not the other). This seemed somewhat surprising because the clinical evidence has shown that both upper and lower fields are mapped eccentrically in the colour centre, located in ventral occipital cortex (*see above*). Either we and the clinical evidence had been wrong, or the new stimulus technique used for detecting cortical activity by phase encoding was inadequate, or the results that it provided had been misinterpreted because the method had actually revealed a novel area posterior to the colour selective region including V4, without detecting V4 at all. The phase encoding method itself is new and not above suspicion, at least for the present. While it works in theory, recent evidence suggests that it may not be quite so reliable in practice. Studies using simple visual stimuli that span the whole visual field and which are turned on and off with a period of about one minute show that similarly considerable variations in cortical response phase are present even when the stimulus is not changing in retinotopic position (i.e. not expanding or rotating) (Guy *et al.* 1999). At the very least, these 'physiological' phase variations, which reflect inherent and varying response delays across the cortex, may contaminate phase-encoding methods. At worst, they may lead to artifactual retinotopic maps. The dazzling visual presentation of the results obtained by this method, achieved through considerable graphic post-processing, may lull one into a sense of security. In fact, it is important to consider these maps in comparison to those obtained by the standard approach, and with some caution. In the case of the human ventral extrastriate cortex, the novel phase encoding method has, to date, only confirmed what had been described before with standard techniques, and it failed to detect even the retinotopic organisation of V4 until this had already been detected by more pedestrian methods (McKeefry and Zeki 1997); it was obviously not designed to detect the presence of non-retinotopically organized visual areas such as V4α (see below). It is perhaps a little disconcerting that groups such as ours and others (Kastner *et al.* 1998), using the

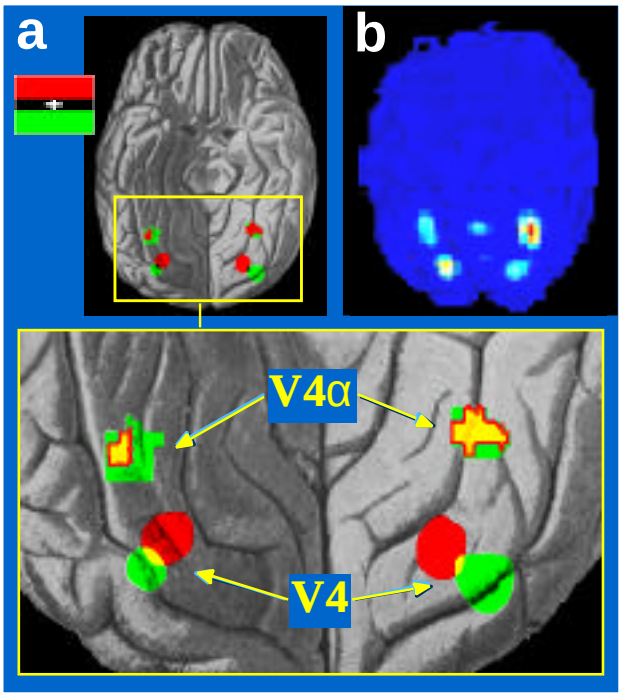

Figure 1

The two components of the V4-complex, the posterior, retinotopically organised area V4 and the anterior area V4α as revealed by the re-analysis of the V4 mapping study by McKeefry and Zeki (1997) (**a**) Projection of the activity obtained by either upper field (in red) or lower field (in green) stimulation with colour vs achromatic onto a ventral view of a human brain (yellow represents the overlap between red and green). For V4 (bottom), the statistical parametric map (SPM) of the following comparison is projected onto the drawing: superior coloured vs. [superior achromatic + inferior coloured + inferior achromatic]. Simpler comparisons revealed the same retinotopic organisation of V4, but this one revealed it most clearly (group of four subjects; threshold: Z=4.81, p<0.05 corrected for multiple comparisons, equivalent to p<0.000001 uncorrected. Coordinates for V4 were as follows (Brains were normalized to the echo-planar imaging (EPI) template provided in SPM, which is similar to the average of 305 brains provided by the Montreal Neurological Institute; Z-scores are given for the hottest voxel): representation of upper visual field (in red): left: (-22,-72,-12) Z>7.31), right: (20,-72,-10) Z>8.46; representation of lower visual field (in green): left: (-30,-76,-8) Z>8.13, right: (32,-76,-10) Z>5.52. For V4α (top), SPMs of a comparison of color vs achromatic stimuli within the corresponding hemifield is projected onto the drawing (threshold: Z=3.09, p<0.001 uncorrected. V4α withstood the corrected threshold for the comparison colour vs achromatic for the whole visual field. Coordinates for V4α were as follows: left: (-34, -54, -14) Z>5.18, right: (30,-50,-20) Z>5.36). (**b**) An independent component analysis (ICA) separates spatially independent maps of brain activity without *a priori*

knowledge about the stimulus conditions. ICA isolated the complete V4-complex, including the posterior (V4, bottom) and the anterior (V4α) subdivisions in both hemispheres, shown here in the glass-brain view of a single subject's brain. This indicates that activity in the complete V4-complex is independent of activity in other cortical areas, and that V4 and V4α are cooperatively activated in this colour task.

standard techniques, have not been able to confirm the existence of area "V4v". The fact that none of the studies using this novel phase encoding technique attach any statistical values to the significance of the presented maps - a basic and stringent requirement for the standard approach - makes it difficult to judge its reliability and the results that deviate from those obtained by standard techniques. It is also somewhat surprising to find that successive maps from the same group have significant, but uncommented on, differences (compare Sereno *et al.* 1995, Tootell *et al.* 1997a, Tootell *et al.* 1997b, Hadjikhani *et al.* 1998).

The notion that, in spite of the clinical evidence only one half of V4, representing upper visual fields only, may be located in the fusiform gyrus within ventral occipital cortex, drove us to reinvestigate the problem of the visual field representation within V4, using the same multi-coloured Mondrian stimuli but this time restricted to stimulation of upper or lower hemifields and detecting BOLD changes with fMRI. Our results (McKeefry and Zeki 1997) showed that upper and lower quadrants are separately mapped within V4, the colour centre (**Figure 1a**); this not only confirmed the clinical conclusions about the nature of visual field representation within V4, but also showed that the apparent sophistication of new stimulation methods, indeed of all new methods, must be regarded with caution. Prior to the study of McKeefry and Zeki (1997), the phase-encoded retinal stimulation method had suggested that there is no colour centre in the ventral occipital lobe of the brain with a complete representation of the contraletral field of view. Our results, derived from the simpler stimulation method, subsequently led to a reexamination by Hadjikhani *et al.* (1998) of the activity produced by colour stimuli, using phase-encoded retinal stimulation. They identified the same area as our V4, in terms of Talairach coordinates, and confirmed that both upper and lower quadrants are indeed separately and contiguously mapped within it. But by describing their area as being "previously undifferentiated" and attaching a new name, "V8", to it, they gave the misleading impression of having discovered a new area; in fact, it is the same area as our V4 and accepted as such by Tootell and Hadjikhani in a personal communication in their

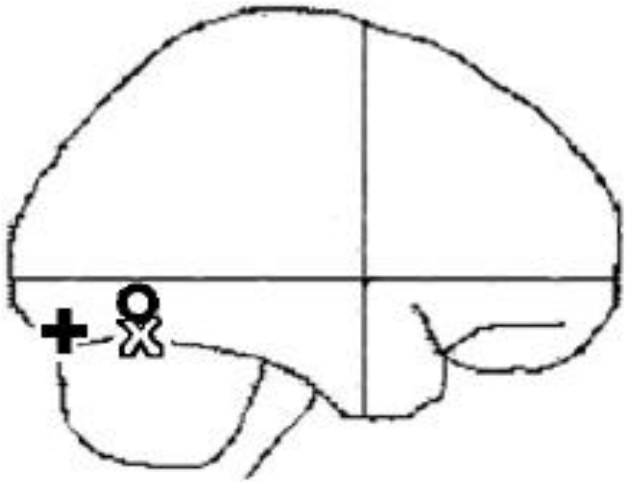

Figure 2

The figure shows the locations of 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.* 1989, Zeki *et al.* 1991, McKeefry and Zeki 1997); **X** corresponds to the "new" area "V8" of Hadjikhani *et al*. (1998) and the + to the area V4v defined by Sereno *et al*. (1995).

statement that "We assume that the cortical area described by McKeefry and Zeki (1997) is equivalent to our area V8, .." (Hadjikhani *et al.* 1998, Tootell and Hadjikhani 1998, Zeki *et al.* 1998) (see **Figure 2**). It does not, therefore, provide any more hope than our earlier discoveries that the cortical processes underlying the conscious perception of colour will be understood better now, as supposed by (Heywood and Cowey 1998), than when we had first described the location of the colour centre in the human brain a decade ago.

The fact that clinicians should have reached, through their observations, conclusions about the nature of the visual field representation within the colour centre long before scanners were put to use to measure cerebral blood flow as a measure of cortical activity is perhaps the most eloquent testimony of all of the importance and primacy of simple clinical observation in detecting and measuring brain activity.

5. THE CLINICAL FATE OF CEREBRAL ACHROMATOPSIA

Clinical evidence has emphasised that cerebral achromatopsia is a complex syndrome (Rizzo *et al.* 1993). In this complexity perhaps lies another cautionary lesson for measuring the brain activity produced by colour with sophisticated new techniques. There are two

issues to consider here, first the nature of the syndrome itself and next the extent of recovery from it, the two being linked.

There is no simple and straightforward condition characterising achromatopsia. This is shown by the fact that, while in some cases (the true achromatopsias), the world is entirely devoid of colour and reported only in terms of "dirty" shades of grey (e.g. Verrey 1888, Young *et al.* 1980), in others (the dyschromatopsias) the defect is less severe; here the perception of some colours may be more affected than others. As examples, the patients of Pearlman (1979) and of Victor (1989) had a greater loss for blues and greens, and a relative sparing for reds (see also Rizzo *et al.* 1993). Allied to this variability is the variability in the degree of recovery. Rather than providing an extensive review of the literature, we offer the following as examples: Ogden (1993), Kölmel (1988), and Paulson (1994) report no recovery in six years, two years and ten months, respectively, after onset whereas Bornstein and Kidron (1959) report a recovery after a few days. Albert *et al*. (1975) report a return of colour vision to one rather than both hemifields, and hence a recovery in one hemisphere rather than both. Moreover, recovery is not invariably uniform, patients often recovering their ability to perceive some colours more than others (e.g. Jaeger *et al.* 1989). This may be the consequence of incomplete lesions (Zeki 1990); Damasio (1985) has suggested that the more a lesion extends posteriorly in the fusiform gyrus, the more severe the defect and the less likely a recovery from achromatopsia. These are of course merely hints and guesses, but our argument in this paper is that hints and guesses derived from clinical evidence are especially worthy of note, and must be critically considered in all measurements of brain activity. That damage to the fusiform gyrus leads to different severities of acquired cortical colour blindness may be merely reflecting the fact that, in some cases, the damage is more extensive than in others; that the syndrome may be characterised by a greater imperception for some colours than for others raises the possibility of subdivisions within the colour centre. The part of the fusiform gyrus activated by colour studies is relatively large and it therefore becomes interesting, in the light of the above clinical observations, to learn whether it is a single uniform area or whether it has subdivisions.

6. V4 AND V4α AS TWO COMPONENTS OF THE COLOUR CENTRE

An examination of the distribution of the most active voxels in our own previous studies of colour activation (**Table 1**) shows a variability. We note here that the figures given in Table 1 refer to the centre points of activity, which covers more extended areas; in fact, the large zone of activation obtained in our first color study on humans (Lueck *et al.* 1989) included all the zones revealed in the subsequent two (Zeki *et al.* 1991, McKeefry and Zeki 1997) and the one reported here.

Table 1. The Talairach coordinates and statistical significance (Z-scores) of the most active voxels in our previous colour activation studies. (Lueck *et al.* 1989, Zeki *et al.* 1991, McKeefry and Zeki 1997)

study and area	*x*	*y*	*z*	*Z-score*
Lueck *et al.* (1989) (PET)				
Left	-27	-56	-5	-
Right	24	-58	-7	-
McKeefry *et al.* (1997) (fMRI)				
Left mean	-29	-68	-14	-
sup field left	-24	-76	-14	4.61
inf field left	-32	-76	-12	4.71
Right mean	30	-75	-19	-
sup field right	28	-72	-12	4.59
inf field right	38	-74	-20	4.71
Zeki *et al*. (1991) (PET)				
Left	-26	-68	-8	-
Right	20	-66	-4	-

We have since undertaken other experiments, to be reported in more detail elsewhere, to study the cortical sites involved in colour vision. These experiments were not actually inspired by the clinical evidence referred to above, but rather by other experimental and clinical evidence (Walsh *et al.* 1993, Kennard *et al.* 1995) which shows that area V4, in man as in monkey, is important for the single most important attribute of the colour system, namely colour constancy. By this we mean the ability of the colour system to "discount the illuminant" (Helmholtz 1911) in which a surface is viewed, since the wavelength composition of the light reflected from a surface changes substantially when it is viewed in light of different illuminants, while the perceived colour remains constant (see also Land 1974). Whatever the inspiration for our recent experiments, the results gain added weight in the light of the clinical evidence regarding the variability in the syndrome of achromatopsia. In these new studies of brain activity related to colour vision, instead of comparing the brain activity produced by a multi-coloured Mondrian with its equiluminous achromatic counterpart, we tried to simulate more nearly a condition in which the Mondrian is viewed while the spectral composition of the illuminating light changes continually, much as would happen when one views a coloured object or surface on a cloudy day with sunny patches, or when viewing coloured surfaces successively

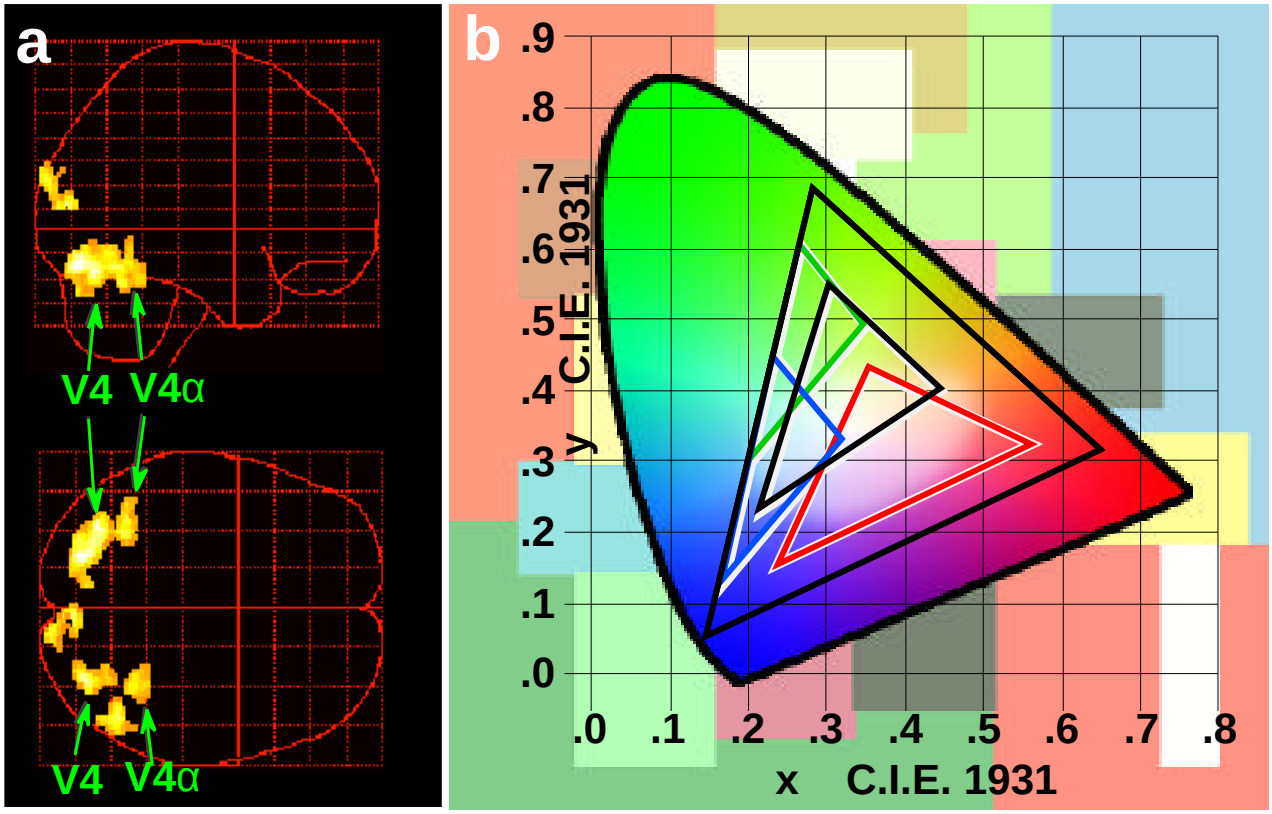

Figure 3

Brain activity elicited when subjects maintain colour constancy while viewing a dynamically changing Mondrian stimulus, that is one in which the wavelength composition or intensity (or both) of the light coming from every square changes continuously. (**a**) The statistical parametric map (SPM) of brain activity for the comparison of the *varying luminance* and the *changing wavelength composition* mode versus the *static* mode in a coloured Mondrian, viewed as a glass-brain shows the two subdivisions of the V4-complex: V4 and V4α (group of six subjects, threshold: Z=3.72, p<0.0001. Tailarach coordinates for V4 were as follows (Z-scores are given for the hottest voxel): left (two peaks): (-34,-68,-18) Z>7.25 and (-22,-76,-16) Z>6.97, right: (34,-74,-16) Z>6.90. Coordinates for V4α were as follows: left: (-28,-54,-18) Z>5.39, right: (28,-50,-16) Z>7.18). There was also very weak activity in the V1/V2 region and lateral to the V4-complex. (**b**) The Mondrian stimulus used is shown in the background. The CIE (Comission Internationale de l'Éclairage) colour flowchart (ellipsoid envelope) is in the foreground. The three inner coloured triangles show the range of the CIE colour space which three Mondrian patches of the corresponding colour would have occupied during the *changing wavelength condition* had they been viewed on their own (the black triangle depicts the same for the white patch). In the experiment, the perceived colour of each patch remained constant, since it was surrounded by other patches and thus viewed in context. The black outer triangle depicts the range of colours our projection screen is capable of displaying.

in light of different illuminants, such as sunlight and tungsten light. We therefore asked subjects to view a coloured Mondrian in three modes. In the first, *static* mode, the wavelength composition of light coming from every patch in the display remained constant throughout the viewing period; in the second, *varying intensity* mode, the Mondrian was viewed in "white light" whose intensity changed continuously, mimicking what would happen if an observer were to view a scene in one illuminant whose intensity varied. Here the total flux at any given wavelength, reflected from every patch, increases or decreases, without altering the wavelength composition, although this would of course necessitate a reassessment of ratios of lights of different wavebands reflected from different patches of the Mondrian. In the third, *varying wavelength composition* mode, we simulated a condition in which the Mondrian is viewed in illuminants whose wavelength composition changed continuously, entailing a change in both flux and wavelength composition of light coming from each square of the Mondrian, without affecting the ratio of light of any given waveband reflected from any two patches and without affecting their perceived colour. We suppose that ratios have to be taken in both the static and dynamic modes, but that the dynamic versions might be the computationally more demanding ones. A comparison of

the brain areas activated by viewing the dynamic and static versions of the Mondrian by using Statistical Parametric Mapping (SPM) (Friston *et al.* 1995) highlighted the region shown in **Figure 3**, known from our previous studies to be colour selective, though without involving nearly as much parallel activation of V1 and V2 as in our previous colour studies. But our dynamic stimuli consistently activated two separate regions within this zone, a larger posterior zone with coordinates very similar to the ones given earlier by us for the human colour centre and a smaller anterior one, not described before (**Figure 3**). We group both, which are separated by ca. 20 mm in the y axis, in the V4 complex, distinguishing V4 proper from the more anterior V4α. We note that in a report that appeared just as the first version of this paper was sent to press, Kastner et al. (1998), in a study of the cortical mechanisms involved in attention, have alluded briefly to much the same organization of the human V4 complex that we describe here, although they use the term TEO for V4α. It would thus seem that the colour centre of the human brain actually consists of two subdivisions, both of which are in some unknown way involved in colour computations. In the future, the complexity of the colour centre as revealed by these relatively new experiments may be one step in accounting for the variability of the syndrome of achromatopsia.

7. REANALYSIS OF EARLIER EVIDENCE

The antero-posterior extent of activation within the fusiform gyrus seen in our earlier studies made us reexamine the earlier evidence. Functional imaging data require currently a minimal spatial smoothing with a full-width-at-half-maximum (FWHM) filter of about twice the resolution of the acquired images in order to obtain an acceptable signal-to-noise ratio. The exact choice of the width for filtering the imaging data is more or less arbitrary, but must be guided by reason. There is no conclusive criterion, such as a cortical region positively labelled by the enzyme horseradish peroxidase in anatomical studies, or the certain attribution of a recording site by means of a small lesion passed at the end of a recording session. This creates a special problem for those who use imaging techniques: do they reveal the full extent of an area or is an area, as revealed, composed of two or more areas? Broader filters can improve the statistical significance of the results (and in multi-subject-analyses eliminate inter-subject variations); narrower filters improve the spatial resolution but decrease the signal-to-noise ratio, with the potential cost of missing out on activations that do not reach significant statistical values with such filters. The study reported here, in which we used the minimum filter described above, shows two separate sites of activation (**Figure 3**) within the larger activated zone revealed by our previous studies, which used broader filters. Reason dictates that if the same colour sensitive areas were activated in all these studies, then a reanalysis that uses less spatial smoothing (with FWHM twice the image resolution) should reveal both zones also in the previous studies. Because of our new discovery, we reanalysed the earlier results of McKeefry and Zeki (1997), using less spatial smoothing; this reanalysis revealed two colour selective subdivisions (the activations were significant for $p<0.05$, corrected for multiple comparisons ($Z>4.8$), which corresponds to $p<0.000001$, uncorrected) and also showed that, whereas the posterior subdivision (V4) is topographically organised, the anterior (V4α) is not (**Figure 1a**). The results also showed that the inferior fields are more strongly represented in V4a, since a comparison of the superior colour stimulation vs. superior achromatic stimulation with the inferior colour stimulation vs. inferior achromatic stimulation did not result in an activation of V4α, although the reverse comparison did. We conclude that, in addition to occupying different positions, the two zones of the V4 complex can be distinguished from one another by the presence of a distinct retinotopic map in V4 and its absence in V4α (**Figure 1a**). However, the fact that the inferior fields seem to be more strongly represented in V4α suggests that it may be organised according to different principles. Indeed, a survey of the published clinical literature based on colour perimetry (Kölmel 1988) would have told us that the two quadrants must be separately mapped within the V4-complex because of cases, e.g. Kölmel's patient 1, who had an achromatopsia restricted to one quadrant alone. This is yet another example of perimetric measurement as an indicator of the functional organisation of the visual brain.

The arrangement of the human V4-complex that we describe here is similar to the one found in the V4 complex of the macaque, an issue which does not fall within the purview of this article, and which we will discuss in greater detail elsewhere. It is worth emphasising here that the two subdivisions of the V4 complex were revealed by relatively simple stimulation techniques. The more sophisticated ones of phase reversal revealed the topographic organisation of V4 itself only after it had been revealed by our technique, and to date have failed to reveal the anterior subdivision of the V4 complex, area V4α, probably because it lacks a retinotopic organisation.

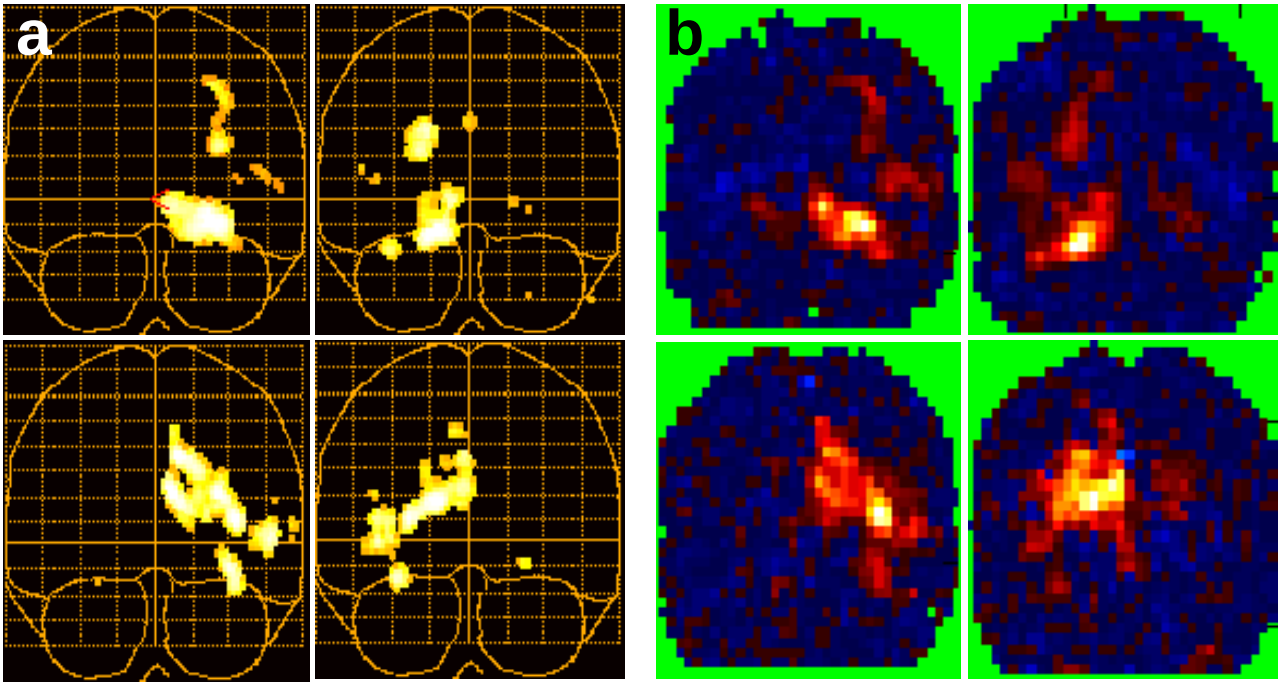

Figure 4

Analysis of data by SPM and ICA revealed that attention to the different quadrants of the visual field co-activated several visual areas in a retinotopic fashion. Coronal views of glassbrain projections derived from (**a**) an SPM analysis in one subject, the comparison being [attention to colour and motion in one quadrant vs attention to both attributes in the remaining three quadrants], thresholded at $p<0.05$ and corrected for multiple comparisons) and from (**b**) an ICA of data from the same subject; the components are those whose time courses correlated most with the conditions in which the subject paid attention to colour and motion in the respective quadrants. The brains are arranged such that the one depicting attention to the top right is located in the top right etc. Almost identical data were obtained in the other four subjects taking part in this study (not shown).

8. THE DETECTION AND MEASUREMENT OF COOPERATIVE ACTIVITY USING INDEPENDENT COMPONENT ANALYSIS (ICA)

In the macaque monkey, the colour pathways leading to the V4 complex are relatively well charted. They include areas V1 and V2, and similar pathways have been found in the human brain, any one of which could be involved in the ratio taking operations that are critical for the generation and construction of colours. The reciprocal connections between these areas (Zeki and Shipp 1989, Nakamura *et al.* 1993, Rockland *et al.* 1994) make it equally likely that the operation is a cooperative one involving all these areas; this is especially so since, in monkey, the wavelength selective cells of V1 are indifferent to the colour of the stimulus but sensitive to changes in the wavelength composition of the light reflected from their receptive fields (Zeki 1983). A distributed ratio-taking process would mean that the results of the operations undertaken at different sites are reported to the perceptual site, area V4, damage to which causes the syndrome of cerebral colour blindness or achromatopsia. In fact, we were surprised to see so little activity in V1 and V2 in response to our dynamic stimuli. Our results thus suggest that the ratio-taking process that is at the heart of the colour generating mechanism is localised to the V4 complex, the key area which, when damaged, leads to cerebral achromatopsia, with the implication that the processing and perceptual sites for colour vision are one and the same (see also Zeki and Bartels 1999).

This raises an important problem of measurement. Our imaging evidence, in seemingly excluding V1 and V2 from the ratio-taking operation, gave us a counter-intuitive result. But it also emphasised the importance of trying to map cooperative activity in a system which is itself cooperative or at least inferred to be so from the richness of its reciprocal anatomical connections. Every area of the cortex has multiple inputs and outputs, and the results of the operations performed by each must therefore be of interest to several others. But not all these recepient areas may necessarily be interested in the result of every operation performed by a given sending area. A very recently developed method, the Independent Component Analysis (ICA) (Bell and Sejnowski 1995),

can be used to isolate spatially independent maps of brain activity (McKeown *et al.* 1998). This algorithm, based on information theory, has the advantage that it is capable of decomposing or unmixing a signal which is a mixture of several other independent signals without any knowledge about the nature of the signal or its sources; it can thus be used to isolate spatially independent maps of brain activation without *a priori* knowledge about the stimulation. In fMRI experiments, one would assume the total brain activity to consist of a mixture of different maps, each fluctuating in a different manner over time, some caused by transient or consistent task-related activity, others by task-unrelated activity, noise and artefacts. If two brain areas are cooperating and therefore give rise to a consistent spatial activity pattern within or throughout the scanning period, one would expect ICA to separate them from other activity patterns; if a third area is coactivated with them only during some periods, ICA would isolate both the doublet and the triplet of areas as two independent activity patterns, representing two different activity maps of the brain. One cannot, naturally, assume different sites of activity within a single brain to be truly independent of each other, and the poor temporal resolution of image acquisition of 4s and inherent differential response delays of the BOLD contrast impose further restrictions. It was therefore gratifying that, amongst the areas isolated by ICA in 6 out of 10 subjects, V4 and V4α were the only ones which occurred as pairs in ventral occipital cortex, suggesting that they can function cooperatively as a single unit, without involvement of other areas (**Figure 1b**). That ICA did not isolate areas V1 and V2 together with V4 and show them to be cooperatively involved in the ratio-taking process nevertheless remains a puzzle, given the anatomical and physiological organisation of the pathways leading to V4, at least in the monkey. Similarly surprisingly, SPM showed that activity in V2 and V1 correlated only minimally with the more demanding ratio-taking tasks (the dynamic conditions) that activated the V4 complex so intensely (**Figure 3a**). It is therefore worth asking whether ICA is capable of always isolating areas that are cooperatively involved.

A simple check on this is to study another colour task and learn whether there is any hint of a cooperative involvement of V1-V2 on the one hand and V4 on the other which can be detected by ICA. Selective attention to colour or to motion activates selectively the centres specialized for those attributes, the V4-complex or the V5-complex, respectively (Corbetta *et al.* 1991). We wanted to learn whether attention modulates the entirety of an area devoted to the attribute being attended to or whether there is a retinotopy of attentional modulation. Moreover, we wanted to learn whether early visual areas such as V1 and V2 would be modulated by attention as well, especially since earlier hypotheses, based on strictly anatomical and physiological criteria, had posited a crucial "window of attention" role for the topographically organised area V2 (Shipp and Zeki 1989). The details of our attentional experiments are to be described elsewhere; in brief, it involved subjects fixating a central cross on a TV monitor while four squares, each containing both colour and motion and arranged so as to stimulate each of the four quadrants of the visual field, separately but simultaneously, appeared on the screen. The subjects' task was to attend to one attribute, *i.e.* colour or motion, in one of the quadrants of the visual field while fixating the central cross. The statistical analysis using SPM shows that several visual areas, including areas V2 and V4, are activated in a retinotopic fashion, when comparing brain activities obtained by attention to the different locations (**Figure 4a**). ICA isolated very similar maps of activation whose time-courses correlated with attention to different quadrants (**Figure 4b**). With attention to colour, SPM showed that both the V4 complex and V2 significantly covary with the task (**Figure 5a**), and ICA isolated an independent activity map in which the V4 complex is cooperatively active together with area V2 (whose time course correlates with the corresponding task) (**Figure 5b**). A comparison, using SPM, of the cortical activity produced by attention to upper and lower field, respectively, showed that attention does not activate the whole of V4 but only those parts of V4 which represent the part of the field of view attended to; there is consequently a retinotopic modulation of V4 by attention (**Figure 5c,d**). Thus our failure to detect any significant activity within V1 and V2 in imaging studies that were designed to detect the cortical site of the ratio-taking operations in colour vision cannot be due to an inadequacy of the use of SPM or ICA. Whatever the explanation for the coactivation of V2 and the V4 complex in some visual tasks and the absence of such coactivation in others, the results given not only open up, we believe, a new field of enquiry into the precise roles of areas V1 and V2 in colour vision (*see below*), but also show that seemingly subjective experiences like attention, which enhance the percept of given attributes at given locations, can be mapped on the cortex, and thus measured, with an unimagined precision, given the strong association of attentional mechanisms to attributes and, apparently, to topographic location as well. We emphasise that the determination of cooperative activity is likely to become of increasing importance in the future (Büchel *et al.* 1999) and we therefore hope that our study is only a prelude to further, more intensive, studies of the organisation of the cerebral cortex. We emphasise, too, that SPM and ICA have revealed subdivisions which sophisticated techniques of stimulation and analysis using phase reversal and presentation on unfolded cortices have failed to show.

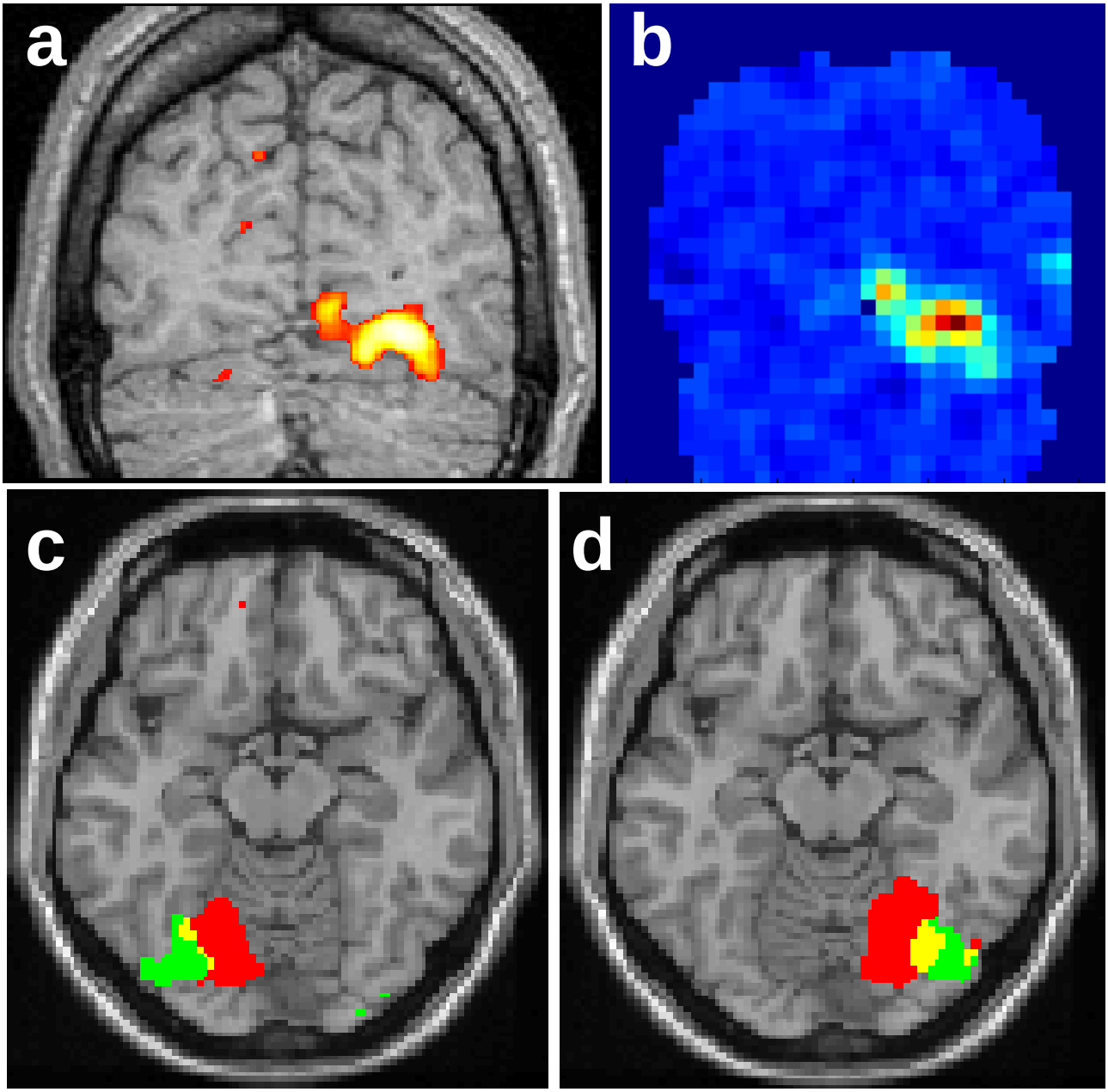

Figure 5

Co-operative activity in areas V4 and V2 and the retinotopic modulation of activity in V4 evoked by attention to quadrants in the upper and lower fields of view. (**a**) A coronal slice taken through an SPM, superimposed on a structural image of a single subject at y=-72 mm (coordinates as described in figure 3) for the comparison [attention to colour in the top left vs. attention to motion in all four quadrants] and thresholded at $p<0.001$, uncorrected. V2 is medial, V4 more lateral. (**b**) ICA isolated the same pattern of co-activation between areas V2 and V4 as revealed by SPM. The slice is taken at the same depth in the same subject for the independent component whose time course correlated most with the condition in which the subject payed attention to colour in the top left quadrant. (**c** and **d**) Retinotopic modulation of V4 by attention to quadrants in the upper and lower hemifields. Horizontal slices were taken through SPMs at z = -14 mm for the contrasts [attention to both colour and motion in one quadrant vs. attention to both attributes in the remaining three quadrants] (5 subjects, $p<0.001$, uncorrected; red: top quadrant, green bottom quadrant) for quadrants within the right (c) or left (d) hemifields. Note the distinctly topographic organization of the activity produced, which respects the topography of V4 as determined in previous studies (McKeefry and Zeki 1997). The medial part of the red patches almost certainly includes area V2 which, at this ventral level, represents the upper quadrant (see a and b).

9. THE RESIDUAL COLOUR VISION OF CARBON MONOXIDE POISONED PATIENTS

Clinical evidence has reported another remarkable phenomenon, namely the relative sparing of colour vision in carbon-monoxide poisoned patients. The first such evidence was reported by Wechsler (1933) and, so improbable were his conclusions, that his findings too were relegated to oblivion for many years, though they have been confirmed several times over in more recent times (for a review, see Zeki 1993b). Wechsler based his conclusions on an observation of a thirteen year old boy of high intelligence who had been admitted to hospital after being overcome by smoke during a fire at his home which had claimed the lives of five members of his family. He had been unconscious for two hours when admitted. Upon recovery, he was found to be mentally retarded and severely impaired visually. "The patient could not recognize small objects, such as a coin, key, pen or watch, and large objects, such as a book, newspaper or telephone, he could distinguish with difficulty". His depth vision may also have been affected, for "He groped in trying to grasp objects, and sometimes collided with persons and things, apparently because he could not estimate distance and probably as a result of a defect in visual spatial discrimination. ... Color perception, on the other hand, was quick and accurate. He recognized not only all primary colors, but such shades as brown and pink. He knew at once the colors of small objects which he could neither name nor tell the form of. He picked out colors on command."

How to account for this bizarre syndrome? Wechsler wrote: "If color vision resides in the cortex and the surface of the brain was destroyed by the pathologic process, color vision should have been lost and not retained. The most probable answer is that either certain parts of the cortex or the layers presumed to perceive and elaborate color vision escaped destruction or they recovered while the visual areas did not. It is barely possible that there are special color-conducting fibers, but all evidence at hand points to the cortex as the seat of color vision. In any event, the case herein presented warrants the statement that color vision and visual acuity can be dissociated in such a way that the former is preserved while the latter is impaired".

The observation is an interesting one and needs to be accounted for in terms of the organization of the visual brain. One suggestion (Zeki 1990) is that the divisions of V1 that are rich in wavelength selective cells, the blobs, are known to be much more richly vascularised (Zheng *et al.* 1991) and are therefore more protected from the effects of hypoxia. The suggestion is not entirely satisfactory, if only because there are examples of reversible vascular insufficiency which are selectively accompanied by muscular weakness and reversible achromatopsia (Lapresle *et al.* 1977). Whatever the explanation, the condition is sufficiently interesting to merit further study. If the above suggestion has any validity, then there are two possibilities. One is that the cells within blobs, being protected from the effects of hypoxia, have outward projections and these relay to V2 and to the V4 complex more or less normally, thus enabling the latter to undertake its task of constructing colours more or less normally. The other possibility is that area V4 is also damaged, with the consequence that the colour vision of such patients is wavelength based, since the responses of cells within the blobs of area V1 and within the thin stripes depend upon wavelength composition, and hence do not correlate with perceived colour (Zeki 1983). If the latter explanation is correct, then such a patient would not exhibit the phenomenon of colour constancy. In fact a recent clinical examination of a patient with a syndrome identical to that described by Wechsler but produced by a prolonged cardiac arrest (Humphrey *et al.* 1995) revealed that his colour vision was indeed very much wavelength based in that, for example, a green surface that reflected a great deal more long wave light appeared red or white to him, not green as it appears to normals (Zeki, Aglioti, McKeefry and Berlucchi, in preparation). A study of the brain areas activated when this patient viewed coloured squares on the screen, compared to conditions when he viewed their achromatic counterparts, revealed that the activity was localised to the calcarine cortex, presumably area V1. The absence of activity in V4 points to another weakness of imaging studies, in that we still do not have a clear idea of what measure of cortical activity to take as significant. But the imaging of activity in a patient suffering from a syndrome described over sixty years ago has important consequences for deciding whether, and to what extent, activity in area V1 can contribute directly to conscious visual experience (Kulikowski *et al.* 1994, Crick and Koch 1995, Zeki and Bartels 1999). This problem is rendered even more emphatic by other clinical studies which show that patients rendered achromatopsic by lesions to V4 can discriminate remarkably well between lights of different wavelength, though without being able to attribute colours to them (Victor *et al.* 1989, Vaina 1994). In this, V4 damaged patients differ markedly from patients suffering from carbon monoxide poisoning, who can discriminate and name colours, even if for them the colours are very much wavelength-

based. The point that we are making is that simple clinical measurements and observations are a rich source of material to guide the measurement of brain activity with more sophisticated methods.

10. CONCLUSION

We have tried, in this study, to emphasise a point which seems to be important to us: that in these days of increasing sophistication in the instruments that are able to detect and measure cortical activity, a high and honourable place must still be reserved for a much simpler and older technique, that of clinical observation. Ignorance of clinical findings can lead to misconceptions, as in the supposition that the lower occipital cortex can only represent upper visual fields. It is evident that no degree of measuring sophistication can guarantee a corrective to such misconceptions. Acquaintance with the clinical literature can on the other hand lead to more searching questions, to which instrumentation must always be subservient.

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