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Selectivity of human retinotopic visual cortex to S-cone-opponent, L/M-cone-opponent and achromatic stimulation

Kathy T. Mullen,[1] Serge O. Dumoulin,[1,*] Katie L. McMahon,[2] Greig I. de Zubicaray[2] and Robert F. Hess[1,3]
[1]McGill Vision Research (H4.14), Department of Ophthalmology, McGill University, 687 Pine Ave. West, Montreal, Canada H3A 1A1
[2]Centre for Magnetic Resonance, The University of Queensland, Brisbane, Australia
[3]School of Optometry, Queensland University of Technology, Brisbane, Australia

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Abstract

Our aim was to make a quantitative comparison of the response of the different visual cortical areas to selective stimulation of the two different cone-opponent pathways [long- and medium-wavelength (L/M)- and short-wavelength (S)-cone-opponent] and the achromatic pathway under equivalent conditions. The appropriate stimulus-contrast metric for the comparison of colour and achromatic sensitivity is unknown, however, and so a secondary aim was to investigate whether equivalent fMRI responses of each cortical area are predicted by stimulus contrast matched in multiples of detection threshold that approximately equates for visibility, or direct (cone) contrast matches in which psychophysical sensitivity is uncorrected. We found that the fMRI response across the two colour and achromatic pathways is not well predicted by threshold-scaled stimuli (perceptual visibility) but is better predicted by cone contrast, particularly for area V1. Our results show that the early visual areas (V1, V2, V3, VP and hV4) all have robust responses to colour. No area showed an overall colour preference, however, until anterior to V4 where we found a ventral occipital region that has a significant preference for chromatic stimuli, indicating a functional distinction from earlier areas. We found that all of these areas have a surprisingly strong response to S-cone stimuli, at least as great as the L/M response, suggesting a relative enhancement of the S-cone cortical signal. We also identified two areas (V3A and hMT+) with a significant preference for achromatic over chromatic stimuli, indicating a functional grouping into a dorsal pathway with a strong magnocellular input.

Introduction

Recent functional magnetic resonance imaging (fMRI) cortical mapping methods have shown that early human visual cortex is divided up into a number of retinotopically organized visual areas that broadly resemble the overall organization found for nonhuman primates (Engel *et al*., 1994, 1997b; Sereno *et al*., 1995; Tootell *et al*., 1998, 2003; Brewer *et al*., 2002, 2005), although human variations are emerging (Hadjikhani *et al*., 1998; Tootell & Hadjikhani, 2001; Brewer *et al*., 2002, 2005). Extensive primate research over several decades has shown that these areas have different functional specializations; however, our understanding of these for the human brain is still at an early stage. In this paper we address the degree of specialization of the different retinotopic visual areas for human colour vision.

Our first aim was to compare the relative fMRI responses of the early visual cortical areas to stimuli designed to activate selectively the achromatic (Ach), long- and medium-wavelength-absorbing cone (L/M-cone) opponent (red–green; RG), or short-wavelength-absorbing cone (S-cone) opponent (blue–yellow; BY) visual pathways under equivalent conditions. This allows us to determine the degree of chromatic and achromatic selectivity of the human visual areas as well as any differential sensitivities between the two colour pathways. This aim raises the issue of the contrast metric used for the presentation of the chromatic and achromatic stimuli. As the fMRI response is typically contrast-dependent, the contrast levels chosen for the three stimulus types will influence the relative cortical responses obtained and any comparison between them. Thus our second aim was to determine which of two contrast metrics better predicts the fMRI response. One metric, often used psychophysically, is to present all stimuli at equivalent multiples of their own detection threshold as a means of scaling stimuli for contrast sensitivity differences and, at least approximately, matching stimulus visibility. It is unclear, however, at what cortical level both threshold and stimulus visibility are determined, hence this metric may not be appropriate for comparing the responses of early visual cortical areas. Alternatively, chromatic and Ach stimuli may be equated directly in terms of contrast, in which case they have different visibilities. This contrast metric represents the contrast of the stimulus to each of the three cone types in human vision and so, like detection threshold, is biologically based but yields visual response at the first stage of vision (the receptors) rather than the higher stage of visibility (threshold). The determination of the contrast metric that better predicts the fMRI response thus raises fundamental questions about the level at which stimulus detectability and visibility are determined.

Previous fMRI studies have revealed responses to colour in the visual cortex (McKeefry & Zeki, 1997; Hadjikhani *et al*., 1998; Bartels & Zeki, 2000; Wade *et al*., 2002; Brewer *et al*., 2005) but very few have

Correspondence: Dr Kathy T. Mullen, as above.
E-mail: kathy.mullen@mcgill.ca

**Present address*: Department of Psychology, Stanford University, Stanford, CA, USA.

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aimed to separate and quantitatively compare the two cone-opponent and the achromatic responses by taking contrast into account (Engel *et al*., 1997a; Liu & Wandell, 2005). In this paper we determine the selectivity of the different retinotopic cortical areas to L/M opponent, S-cone, and Ach activation in two different experiments, one in which stimuli are matched in multiples of detection threshold (MDT), and the other in which stimuli are matched in terms of absolute (cone) contrast (AC). This allows us to determine quantitatively whether the different visual areas have colour or achromatic preferences and the relationship of these preferences to the metric used.

Materials and methods

Subjects

Eight healthy observers were used as subjects (four female; mean age 41, age range 31–54 years), five of whom were naive as to the purpose of the study. The subjects were instructed to maintain fixation on the fixation point provided and trained prior to the scanning sessions to familiarize them with the task. All observers had normal or corrected-to-normal visual acuity. No participant had a history of psychiatric or neurological disorder, head trauma or substance abuse. Informed written consent was gained from all participants prior to the commencement of the study. The study was conducted within the constraints of the ethical clearance from the Medical Research Ethics Committee of the University of Queensland for MRI experiments on humans at the Centre for Magnetic Resonance.

Visual stimuli

The stimulus consisted of a circular sine-wave grating [0.5 cycles per degree (c.p.d.)] whose contrast phase reversed at 2 Hz, presented in a temporal Gaussian contrast envelope (sigma = 125 ms). Three different stimuli were used (RG, BY and Ach) that isolated the L/M-cone-opponent, the S-cone-opponent and the Ach (luminance) postreceptoral mechanisms, respectively. [We use the colour terms 'RG' and 'BY' to refer to the stimuli that activate L/M-cone-opponent and S/(L + M)-cone-opponent mechanisms, respectively. These mechanisms, when activated selectively by the cardinal stimuli, do not give rise to the unique colour sensations of red, green, blue or yellow and so should not be confused with the colour-opponent processes.] The contrast of the stimuli was matched either in cone contrast or in MDT, as described below. The circular stimulus was seen as 16° (full width) by ~ 12° (full height), as stimulus height was limited top and bottom by the subject's placement in the magnet bore.

Chromatic representation of the stimuli

The chromaticity of the stimuli was defined using a three-dimensional cone contrast space in which each axis represents the quantal catch of the L-, M- and S-cone types, normalized with respect to the white background (i.e. cone contrast). Stimulus chromaticity is given by vector direction and contrast by vector length within the cone contrast space and so they are device-independent. Three cardinal stimuli (RG, BY and Ach) were determined within this space to isolate each of the three different postreceptoral mechanisms. A cardinal stimulus isolates one postreceptoral mechanism and is invisible to the other two, and is defined as the unique direction orthogonal in cone contrast space to the vector directions representing the other two postreceptoral mechanisms (Cole *et al*., 1993). We selected our three cardinal stimuli from the knowledge of the cone weights of the three postreceptoral mechanisms provided by earlier studies (Cole *et al*., 1993; Sankeralli & Mullen, 1996, 1997), and they have the following directions in the cone contrast space: the Ach stimulus activates L-, M- and S-cones equally (weights of 1, 1 and 1, respectively); the BY stimulus activates S-cones only (weights of 0, 0 and 1); and the isoluminant RG stimulus activates L- and M-cones opponently in proportions determined by the isoluminant point and has no S-cone activation (weights of 1, –a and 0) where a, the ratio of L- to M-cone weights for RG isoluminance, was determined individually for three of our eight subjects (KTM, SOD and RFH) using a minimum motion method (Cavanagh *et al*., 1984) for a patch of binocularly viewed RG grating (0.5 c.p.d., 3.6 ^{o2}) and was based on the mean of 10 settings per subject. The average of these three isoluminant points was used for the remaining five subjects (see Table 1). Detection thresholds for the RG, BY and Ach stimuli (0.5 c.p.d., radius 10°) were measured using a temporal 2-alternate forced choice (2AFC) staircase procedure for the same three subjects, and were based on the mean of three or four repeats per condition. Detection thresholds for the remaining five subjects were taken as the average for these three subjects for each condition and are given in Table 1.

TABLE 1. Detection thresholds for Ach, RG isoluminant and BY cardinal stimuli as percentage cone contrast for three subjects

	Detection thresholds			
	KTM	RFH	SOD	Average
Ach (%)	0.44 ± 0.05	0.39 ± 0.04	0.43 ± 0.08	0.42 ± 0.003
RG (%)	0.16 ± 0.008	0.17 ± 0.011	0.16 ± 0.02	0.16 ± 0.005
(Iso)	(1 : 3.5)	(1 : 2.6)	(1 : 2.2)	(1 : 2.8)
BY (%)	1.18 ± 0.14	1.30 ± 0.17	1.07 ± 0.04	1.18 ± 0.12

Detection threshold values are mean ± SD. The measured isoluminant point (Iso) for the RG stimuli is given in parentheses as an L : M ratio. The average thresholds and isoluminant point of the three subjects (Average) was used for the remaining five subjects.

Apparatus and calibrations

For all fMRI experiments, the visual stimuli were generated using PsychToobox software (Brainard, 1997; Pelli, 1997) on a Macintosh G3 iBook and displayed on a white screen using an LCD projector (InFocus LP250, resolution 1024 × 768, frame rate 80 Hz, mean luminance 30 cd/m^2). The screen was placed 2.7 m from the subject. For all psychophysical experiments, used to determine detection threshold and isoluminance, stimuli were generated using a VSG 2/5 graphics board with 15-bit contrast resolution (Cambridge Research Systems Ltd, Rochester, England), housed in a Pentium PC computer and displayed on a CRT monitor (Diamond Pro 2030). Both displays were calibrated in the same way. The red, green and blue spectral emissions were measured using a PhotoResearch PR-650-PC SpectraScan (Chatsworth, CA, USA), and the Smith & Pokorny (1975) fundamentals were used for the spectral absorptions of the L-, M- and S-cones. From these data, a linear transform was calculated to specify the phosphor contrasts required for given cone contrasts (Cole & Hine, 1992). Both displays were gamma-corrected in software with lookup tables.

Experimental protocol

The four different stimulus conditions used were Ach, RG and BY stimuli, and a mean luminance (blank) condition in which only the fixation stimulus appeared. In the fixation condition, a white ring surrounded the small black fixation spot. Stimuli were presented time-locked to the acquisition of fMRI time frames, i.e. every 3 s. To control for attention, the subjects continuously performed a two-interval forced-choice contrast-discrimination task, in which a given

presentation consisted of two intervals, both displaying stimuli from the same condition but with a small contrast difference between them. The subject indicated which interval contained the higher-contrast stimulus. The contrast difference ranged between ±10 and ±20% of the mean contrast for each stimulus type, and was selected based on psychophysical measurements on three subjects prior to scanning to yield a contrast discrimination performance above chance but < 100%. The same contrast increments were given to all subjects. Each stimulus was presented within a 500-ms time window in a temporal Gaussian contrast envelope (sigma = 125 ms), with an interstimulus interval of 500 ms. In the remaining 1.5 s the subjects' responses were recorded using an MR-compatible computer mouse. During the mean luminance (blank) condition an identical contrast-discrimination task was performed for the fixation stimulus. The four stimulus types were presented in a counterbalanced block design (six presentations per block, duration 18 s). Each block was repeated 10 times, giving a total of 240 presentations per scan, i.e. 12 min per scan. All results are based on data from two scans per experiment (480 presentations, 24 min). Virtually all subjects' responses ranged between 75 and 100% correct with an overall average of 82% correct (see Table 2).

Two contrast metrics were used in two separate experiments and are illustrated in Fig. 1. In one, detection thresholds for the three stimuli were measured as described above, and all stimuli were presented at equivalent multiples of their respective detection thresholds (×25) to scale for contrast-sensitivity differences. The cone contrasts of these stimuli at ×25 were 11% (Ach), 4% (RG) and 30% (BY), which fall in the upper range of contrast values obtainable within the gamut of the colour space used. In the other contrast metric, stimuli were presented at similar cone contrasts (6.5% for the Ach and BY, and 5% for the RG stimulus). These cone contrasts were not exactly matched due to the 8-bit hardware limitations of the fMRI projection system. All other conditions were the same in the two experiments.

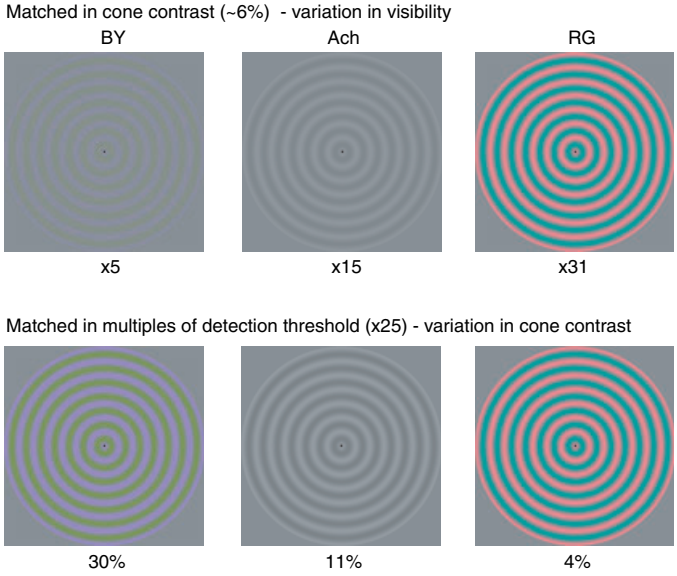

FIG. 1. Examples of the sine-wave ring stimuli used in the experiment, which were calibrated to activate selectively the RG, BY or Ach visual mechanisms. In separate experiments stimuli were presented using two different contrast metrics. In the top panels stimuli are matched in cone contrast (5–6.5%, within hardware limitations; see Materials and Methods). Their corresponding values in MDT are marked below each panel, and are lowest for the BY stimulus and greatest for the RG. In the lower panels, the stimuli are matched in MDT (×25), and are of similar visibility. Their contrast values are marked underneath; the BY stimulus has the highest threshold and so is presented at the highest contrast, whereas the RG stimulus has the lowest contrast detection threshold and is presented at the lowest contrast. Note that the printed images are not an accurate representation of the actual stimuli.

Magnetic resonance imaging

The magnetic resonance images were acquired using a 4T Bruker MedSpec system at the Centre for Magnetic Resonance, Brisbane, Australia. A transverse electromagnetic head coil was used for

TABLE 2. Percentages of correct contrast judgements during the fMRI scans

	MDT	AC
Ach (%)	89 ± 8	81 ± 19
RG (%)	93 ± 9	77 ± 21
BY (%)	91 ± 11	72 ± 20
Fix (%)	92 ± 9	82 ± 17

To control for attention during the fMRI scans, the subjects continuously performed a contrast-discrimination task. The results are mean ± SD percentages and are shown for the achromatic (Ach), isoluminant red–green (RG) and isoluminant blue–yellow (BY) stimuli presented at equivalent MDT or at equivalent AC, and for the fixation (Fix) stimulus. Overall average, 82 ± 9%.

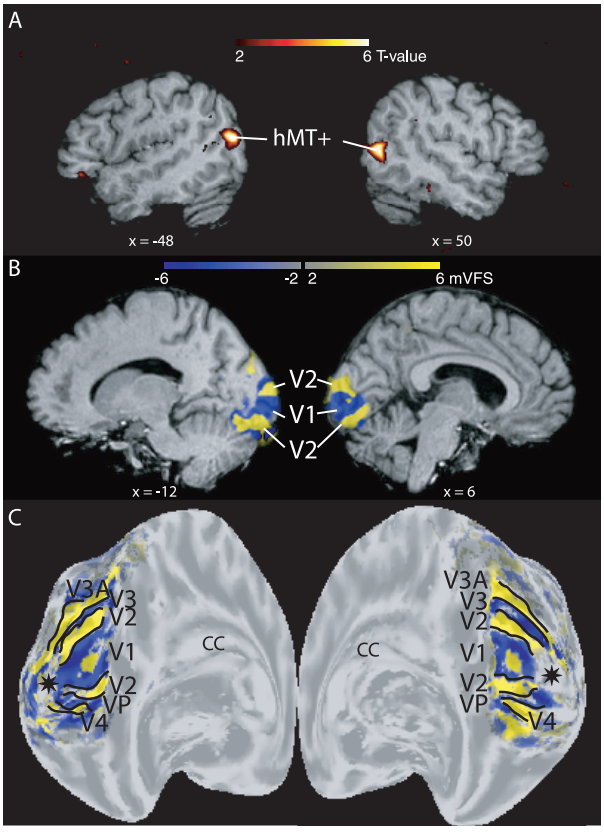

FIG. 2. Example of visual area identifications in the left and right hemispheres, respectively. (A) Example of identification of area hMT+ (subject JS; Dumoulin *et al.*, 2000). (B) Example of volumetric visual field map used to identify visual areas V1–V4 (V1 and V2, subject JS). (C) Example of volumetric visual field maps shown on an unfolded cortical surface (subject RH). The surfaces are shown in a medioposterior viewpoint and the corpus callosum (CC) is identified to facilitate orientation on the surfaces. This surface representation is for illustration purposes only as the areas are volumetrically defined, but it shows all retinotopically defined visual areas that are delineated with lines. The star indicates the location of the foveal confluence.

radio-frequency transmission and reception (Vaughan *et al*., 2002). For the fMRI studies, 241 T2*-weighted gradient-echo echoplanar images depicting blood oxygen level-dependent (BOLD) contrast (Ogawa *et al*., 1990) were acquired in each of 36 planes with TE 30 ms, TR 3000 ms, in-plane resolution 3.6 mm and slice thickness 3 mm (0.6 mm gap). The slices were taken parallel to the calcarine sulcus and covered the entire occipital and parietal lobes and large dorsal–posterior parts of the temporal and frontal lobes. Two or three fMRI scans were performed in each session. Head movement was limited by foam padding within the head coil. In the same session, a high-resolution 3-D T1 image was acquired using an MP-RAGE sequence with TI 1500 ms, TR 2500 ms, TE 3.83 ms and resolution 0.9 mm^3. Identification of the visual areas (early retinotopic areas and MT) were performed in separate sessions with identical parameters except for the number of time frames (128), number of fMRI scans (1–4) and slice orientation (orthogonal to the calcarine for the retinotopic mapping experiments).

Preprocessing of MR images

The anatomical MRI scans were corrected for intensity nonuniformity (Sled *et al*., 1998) and automatically registered (Collins *et al*., 1994) in a stereotaxic space (Talairach & Tournoux, 1988). The initial two time frames of each functional run were discarded due to start-up magnetization transients in the data. All remaining time frames were blurred with an isotropic 3-D Gaussian kernel (4 mm full-width half-maximum) to attenuate high-frequency noise. The functional scans were corrected for subject motion within and between fMRI scans (Collins *et al*., 1994).

Identification of visual areas

Early visual cortical areas were identified using volumetric phase-encoded retinotopic mapping (COBRA package; Dumoulin *et al*., 2003). This methodology has been compared to cytoarchitectonic analysis of the human visual cortex, revealing a good correspondence between functionally and anatomically derived segregations of visual areas (Wohlschlager *et al*., 2005). Standard stimuli were used to create polar-angle and eccentricity maps of the visual cortex (Engel *et al*., 1994; Sereno *et al*., 1995; Dumoulin *et al*., 2003). By combining eccentricity and polar-angle phase maps with the anatomical MRI, the visual field signs of different visual areas could be segmented. Neighboring visual areas could be identified due to opposite field signs, i.e. visual areas V1, V2, V3, VP, V3a and human (h)V4 (Sereno *et al*., 1994, 1995; Dumoulin *et al*., 2003), as illustrated in Fig. 2B and C. Low-contrast Ach flickering stimuli (16 Hz, 1%) contrasted with stationary patterns were used to localize hMT+ (Dumoulin *et al*., 2000; see also Fig. 2A). A region in ventral occipital cortex (VO) was defined functionally as described in Results (VOI analyses).

Statistical analysis

The fMRI data were analysed using software developed by Worsley *et al*. (2002). This statistical analysis is based on a linear model with correlated errors. Runs, sessions and subjects were combined using a linear model with fixed effects and SDs taken from the previous analysis on individual runs. A random-effects analysis was performed by first estimating the ratio of the random-effects variance to the fixed-effects variance, and then regularizing this ratio with a Gaussian filter (10 mm full-width half-maximum). The variance of the effect was then estimated from the smoothed ratio multiplied by the fixed effects variance to achieve higher degrees of freedom. The resulting *t*-statistical images were thresholded for peaks and cluster sizes using random field theory (Worsley *et al*., 1996).

The volume-of-interest (VOI) analysis of the identified visual areas (V1 to hV4, hMT+ and VO) was performed in an identical fashion. Prior to the statistical analysis, the fMRI signal fluctuations were converted to percentage BOLD signal change relative to the mean signal intensity level for the scan on a per voxel basis. For example, −50% and 100% signal change correspond to a half and double, respectively, the mean signal intensity of the fMRI signal. Time series of voxels within a VOI (left and right hemispheres) were averaged together, with exclusion of voxels displaying artifacts. Voxels with artifacts were identified by their unusually large intensity variations in their time series, i.e. voxels with a SD threshold > 19 (although the final results were stable across a range of thresholds). The VOI analysis was performed on each subject's areas and subsequently averaged across subjects. Because the time series were converted to percentage BOLD signal change the effect size of the linear model (β) is also expressed as a percentage signal change. The effect sizes and their SDs are relative to the overall mean of the time series are plotted in Figs 5 and 6.

Results

Surface representations

We first use a stereotaxic representation (voxel-based analysis) to reveal any overall preferences for chromatic over Ach stimuli, or vice versa, across the visual cortex (Fig. 3). For this figure we have included all data for both contrast conditions (MDT and AC) and we have averaged the responses of the two isoluminant chromatic stimuli (RG and BY) to obtain an overall 'colour' response. Data are the average of all eight subjects. The figure shows the oblique medial views of the left and right hemispheres of an averaged unfolded cortical surface in a stereotaxic space (Talairach & Tournoux, 1988; Collins *et al*., 1994) with the positions of the subjects' averaged border locations dividing the early visual areas V1, V2, V3, VP, V3A and hV4, and the probable location of hMT+ marked by dashed lines for reference only. These boundary positions and the foveal representations are based on the averaged retinotopic mapping data of our eight subjects and, as averaged measures, are given for illustration only. The *t*-values represent to the differences between the responses to the Ach stimuli and the chromatic stimuli, with the red–yellow scale indicating a significantly greater response to Ach stimuli and the blue–purple scale indicating a preferential response for chromatic over Ach stimuli.

Our results show quite strikingly the presence of discrete visual cortical regions that respond preferentially to the isoluminant chromatic stimuli over the Ach stimuli (purple–blue scale), and to Ach over chromatic (red–yellow scale). Preferential responses to the chromatic stimuli were found in a large region in medial occipital cortex (MO), corresponding provisionally to V1 and possible parts of V2. In addition, a clear preferential chromatic response was also seen in a region of ventral occipital cortex (marked VO), extending ventral and anterior to the early visual areas. We also defined two cortical regions that showed a strong preferential response to Ach over the chromatic stimuli and that lie in a dorsal occipital (DO) and a lateral occipital (LO) position as marked in Fig. 3. Based on the stereotaxic coordinates and the probabalistic maps, the DO region appears to overlap with area V3A (Tootell *et al*., 1997; Press *et al*., 2001; Dumoulin *et al*., 2003) and the LO region corresponds to hMT+.

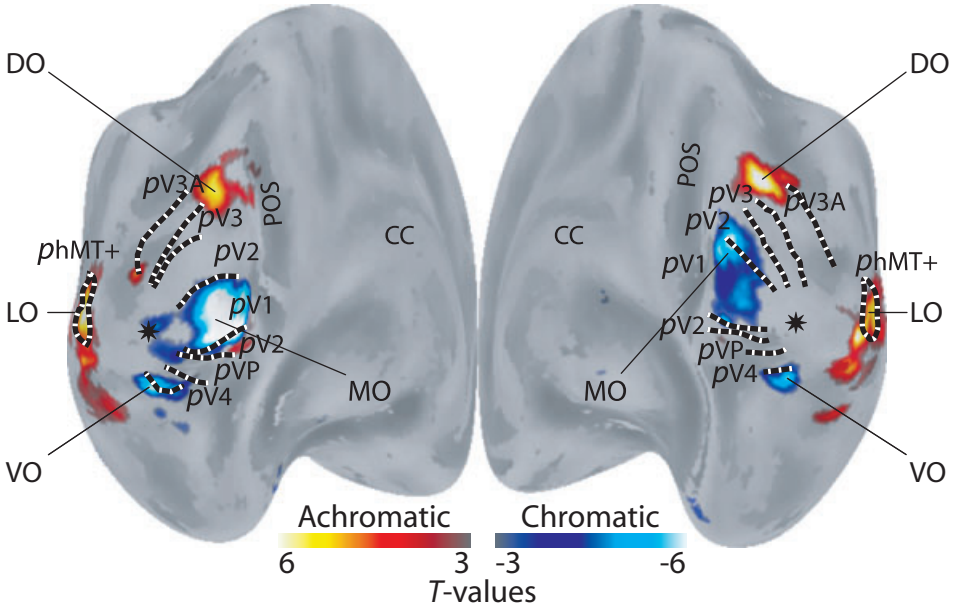

FIG. 3. Average *t*-statistical map ($n = 8$) comparing Ach and chromatic conditions, displayed on average unfolded cortical surfaces. The oblique medial views of the left and right hemisphere are shown on the left and right, respectively. On the averaged surfaces major anatomical structures can be identified (MacDonald *et al.*, 2000) and the locations of the parietal–occipital sulcus (POS) and corpus callosum (CC) are indicated to facilitate orientation on the surfaces. For illustrative purposes, black-and-white dashed lines indicate the average visual area and border locations of the eight subjects (iso-probability lines) and these estimated regions are labelled for V1, V2, V3, VP, V3A, hV4 and hMT+. The stars indicate the cortical representations of the fovea in each hemisphere based on the average of our eight subjects. Significantly stronger responses to Ach than to the average of the two chromatic stimuli are indicated by positive *t*-values (red–yellow scale) and significantly stronger responses to the average of the two chromatic stimuli than to Ach stimuli are indicated by negative *t*-values (purple–blue scale). Areas responding more to chromatic stimuli are found in MO and VO, and those responding more to Ach stimuli are found in both the DO and the LO regions. The coordinates of the peak responding voxel in each of these four regions, and the associated *t*- and *P*-values, are given in Table 2. Response profiles of these peak voxels to the individual RG, BY and Ach conditions, and the two stimulus contrasts levels, are given in Fig. 4.

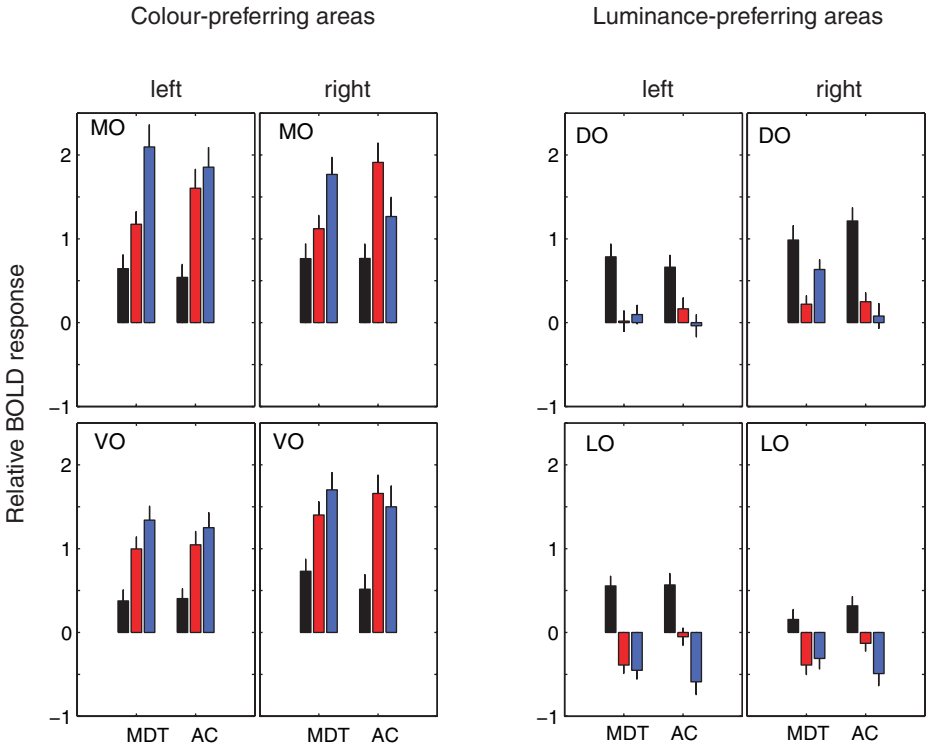

FIG. 4. Responses of the peak voxels to the different stimuli in each of the four preferentially responding regions defined in Fig. 3. Both hemispheres are shown. The ordinate shows the average percentage BOLD signal change and SD for each condition. On the left, results for peak responding voxels in the two colour-preferring areas are shown: MO (putative area V1) and VO. On the right are results for peak responding voxels in the two Ach-preferring areas: DO (putative area V3A) and LO (putative area hMT+). Histograms are colour-coded according to the stimulus used: red, RG stimuli; blue, BY stimuli; and black, Ach stimuli.

In order to provide a more detailed analysis of the data of Fig. 3 and to separate responses according to the different stimulus colour and contrast conditions we identified the local maxima (voxels with peak *t*-values) in each of the four preferentially responding regions in Fig. 3 (selection of 'peak voxels'). The coordinates of the peak voxels are given in Table 3 and their responses across the three stimulus types (RG, BY and Ach) at the two stimulus contrast levels are plotted in Fig. 4. The left group of four panels shows the results for the two colour-preferring regions (MO and VO) and the right group of four panels shows results for the two Ach-preferring regions (DO and LO). Results for the left and right hemisphere of each cortical region are shown. Within each panel, the left group of histograms shows the results for the stimuli presented at equivalent multiples of detection threshold (MDT) and the right group shows results for stimuli presented at equivalent cone contrasts (AC).

For the peak-responding voxels that were colour-preferring we found that the preferential response to chromatic stimuli was consistent across both contrast metrics used, showing that in these cases preference was independent of the contrast metric. We also noted that even though these voxels were selected for their strong preferential chromatic response they still displayed a robust response to Ach stimuli. We also saw that the stimulus set matched in MDT generally produced a stronger response to BY than RG stimuli, whereas for stimuli matched in terms of cone contrast there was no consistent difference between RG and BY responses. We will return to these points subsequently. The peak voxels that were Ach-preferring showed a strong differential response, although there remained in all cases some response to both types of chromatic stimuli.

VOI analyses

The stereotaxic representation in Fig. 3 is limited in its ability to localize different responses to the different cortical areas as it does not define visual areas individually for each subject. To address this issue we used a VOI analysis in order to compare the responses of the identified retinotopic cortical areas to the different stimulus colours and contrasts in each subject. The visual areas were defined for each subject, using retinotopic mapping (V1, V2, V3, VP, V3a and hV4) or flickering stimuli (hMT+). In the case of the region we have termed VO, we used a functional definition in which we include all voxels in the regions surrounding the peak responding voxel that had a *t*-value > 3 on the average data, but this was adjusted for each subject so that no overlap between VO and the retinotopically defined areas (e.g. hV4) existed. Thus VO was defined as a colour-sensitive region that

TABLE 3. Brain regions where a significant difference in response to chromatic and achromatic stimuli was found

Brain region	Coordinates (mm)			*t*-value	*P*-value
	x	*y*	*z*		
Achromatic					
DO					
Right	22	−90	22	6.6	<0.001
Left	−14	−92	22	5.6	0.008
LO					
Right	44	−80	−6	6.5	<0.001
Left	−44	−70	0	6.4	<0.001
Chromatic					
MO					
Right	10	−100	8	6.2	<0.001
Left	−6	−94	−12	7.9	<0.001
VO					
Right	30	−74	−18	5.8	0.003
Left	−32	−74	−14	6.3	<0.001

Peak *t* and corresponding *P* values are listed, corrected for multiple comparisons (Worsley *et al*., 1996; Worsley *et al*., 2002), with their corresponding *x*, *y* and *z* stereotaxic coordinates (Talairach & Tournoux, 1988; Collins *et al*., 1994). Stronger responses to the chromatic stimuli (average of RG and BY conditions) were elicited in medial (MO) and ventral (VO) occipital cortex. Stronger responses to Ach stimuli were found in dorsal (DO) and lateral (LO) occipital lobes.

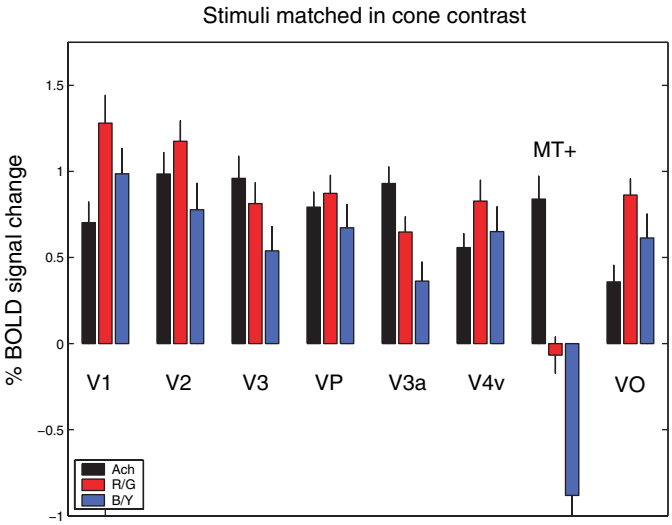

FIG. 5. Results of a VOI analysis for the eight identified visual areas, performed for each subject individually and subsequently averaged across the eight subjects. The ordinate shows the average percentage BOLD signal change and SD for each condition. Results are for the AC condition in which stimuli were matched in cone contrast. Histograms are colour-coded according to the stimulus used: red, RG stimuli; blue, BY stimuli; and black, Ach stimuli. Statistical comparisons are given in Table 4.

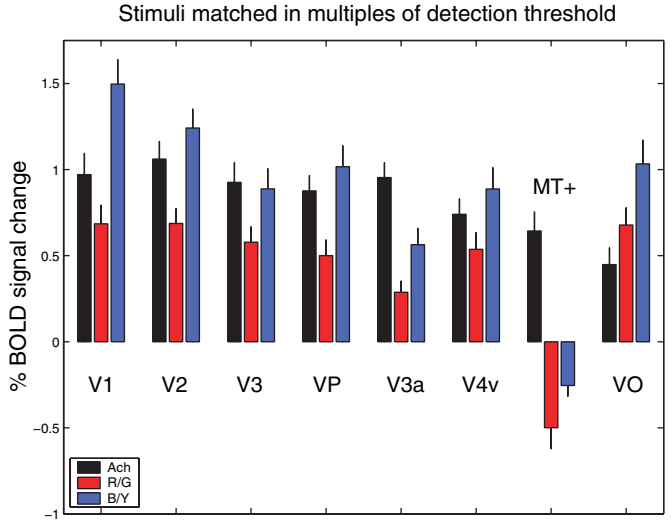

FIG. 6. Results of a VOI analysis for the eight identified visual areas, performed for each subject individually and subsequently averaged across the eight subjects. The ordinate shows the average percentage BOLD signal change and SD for each condition. Results are for the MDT condition in which stimuli were presented at a constant multiple (×25) of their respective detection thresholds. Histograms are colour-coded according to the stimulus used: red, RG stimuli; blue, BY stimuli; and black, Ach stimuli. Statistical comparisons are given in Table 5.

lies beyond hV4 but may contain parts of several ventral occipital visual areas (Brewer *et al*., 2005).

Results are shown in Figs 5 and 6, and Tables 4 and 5 show the *t*- and *P*-values for a multiple *t*-test comparison of the responses using a Bonferroni correction to take into account the multiple comparisons (Worsley *et al*., 1996, 2002). Figure 5 (with Table 4) shows results for stimuli presented at matched cone contrasts and Fig. 6 (with Table 5) shows the results when stimuli are matched in MDT. Considering results for stimuli matched in cone contrast first, we can make a number of key points. Firstly, there were only two visual areas that showed any significant preferences for colour over Ach stimuli. Area V1 had a significantly higher response to RG than to Ach. Its response to the average of the two colour stimuli (Col) was greater than the response to Ach stimuli but fell below significance ($P = 0.06$). We note that the stronger preference for colour shown by V1 in the single voxel data (Fig. 4) compared to the VOI data is probably due to the inclusion of more peripheral regions of the visual field in the VOI analysis. Later in the paper we describe how the relative sensitivity to RG, BY and Ach stimuli varies across eccentricity. VO was the other area with a significantly greater response to Col than to Ach stimuli, corresponding to its definition, and it responded significantly more to RG than to Ach stimuli.

There were two visual areas that showed significant preferences for Ach over colour stimuli. Area V3A had a significantly greater response to Ach than Col stimuli, and a significantly greater response to Ach than BY stimuli. Area hMT+ showed a significant preference for Ach stimuli over both RG and BY stimuli, and their average (Col).

All remaining areas (V2, V3, VP and hV4) had similar responses to RG, BY and Ach stimuli with no significant differences between them. We note that, in all the colour-sensitive areas, responses to the S-cone stimuli were surprisingly robust with no significant differences between the two different chromatic stimuli (RG and BY) despite their large differences in visibility.

Figure 6 (with Table 5) shows the results obtained when stimuli were presented at equal MDT. With this contrast metric we found that the response to BY stimuli became the dominant chromatic response and was significantly stronger than the RG in most areas [V1, V2, V3, V3A, VP and hV4, with VO falling just below significance ($P = 0.06$)] with the exception of hMT+, which had very weak responses to both BY and RG. For the areas that had a strong difference between the BY and RG response it was not meaningful to average the two chromatic responses in order to compare with the Ach stimulus. We thus selected the three areas that had the least difference between RG and BY, V3A ($P = 0.05$), VO ($P = 0.06$) and hMT+ ($P = 0.06$), and compared responses between Col and Ach. Corresponding to the definition of VO, in the VOI analysis it remained a cortical region with a significant averaged chromatic preference whereas V3A and hMT+ remained areas with significant Ach preferences.

When stimuli were equated in MDT, all the visual areas, with the exception of the two Ach-preferring areas (V3A and hMT+), showed a stronger response to BY and a weaker response to RG, with the Ach response in the middle, a ranking that corresponds to the contrast values of the stimuli presented (30, 11 and 4% for BY, Ach and RG, respectively). These responses suggest that contrast directly determines the BOLD response irrespective of stimulus threshold or visibility differences. This issue is explored in the next section.

TABLE 4. Stimuli presented at matched cone contrasts (AC)

	Ach–RG		Ach–BY		BY–RG		Ach–Col	
	t-value	*P*-value	*t*-value	*P*-value	*t*-value	*P*-value	*t*-value	*P*-value
V1	−3.44	<0.001*	−1.24	>0.70	−1.45	0.66	−2.48	0.06
V2	−1.4	>0.70	0.94	>0.70	−2.43	0.07	−0.01	>0.70
V3	0.32	3.38	1.89	0.27	−1.43	0.68	1.46	0.65
VP	−1.05	>0.70	0.79	>0.70	−1.36	>0.70	0.02	>0.70
V3a	2.02	0.19	3.34	<0.001*	−1.86	0.28	3.15	0.01*
V4	−1.9	0.26	−0.44	>0.70	−1.03	>0.70	−1.27	>0.70
hMT+	4.81	<0.001*	7.49	<0.001*	−4.76	<0.001*	6.99	<0.001*
VO	−4.17	<0.001*	−1.09	>0.70	−1.43	0.69	−2.85	0.02*

Data are *t*- and *P*-values for the VOI analyses plotted in Fig 5; *t*-values are for the differences in cortical response between the different stimulus conditions shown (Col, averaged RG and BY). Significant differences (*$P \leq 0.05$) are based on a multiple *t*-test comparison between conditions with a Bonferroni correction for multiple comparisons based on the eight visual areas examined (Worsley *et al*., 1996, 2002). The sign of the *t*-value indicates which response is greater.

TABLE 5 Stimulus contrasts matched in MDT (×25)

	Ach–RG		Ach–BY		BY–RG		Ach–Col	
	t-value	*P*-value	*t*-value	*P*-value	*t*-value	*P*-value	*t*-value	*P*-value
V1	1.86	0.28	−4.51	<0.001*	4.85	<0.001*	−1.25	>0.70
V2	2.8	0.02*	−2.26	0.11	4.39	<0.001*	0.69	>0.70
V3	2.32	0.09	−0.55	>0.70	2.97	0.01*	1.22	>0.70
VP	4.56	<0.001*	−1.05	>0.70	4.37	<0.001*	3.01	0.01*
V3a	5.75	<0.001*	3.8	<0.001*	2.55	0.05*	5.57	<0.001*
V4	1.93	0.24	−1.39	>0.70	3.3	<0.001*	0.35	>0.70
hMT+	5.32	<0.001*	8.19	<0.001*	1.47	0.64	6.5	<0.001*
VO	−1.77	0.34	−3.06	0.01*	2.47	0.06	−2.62	0.04*

Data are *t*- and *P*-values for the VOI analyses plotted in Fig 6; *t*-values are for the differences in cortical response between the different stimulus conditions shown (Col, averaged RG and BY). Significant differences (*$P \leq 0.05$) are based on a multiple *t*-test comparison between conditions with a Bonferroni correction for multiple comparisons based on the eight visual areas examined (Worsley *et al*., 1996, 2002). The sign of the *t*-value indicates which response is greater.

Contrast metric

The key question addressed in the following analysis is whether BOLD responses across the different stimulus conditions (RG, BY and Ach) are better predicted by the metric of cone contrast (AC) or by a threshold-based metric in which stimulus contrast is scaled in MDT, thus eliminating any visibility differences that arise from differences in contrast sensitivity. In the following analysis we compared BOLD responses based on the two contrast metrics used. To assess which cortical regions covary with either of the two contrasts metrics, we correlated the fMRI signals elicited by the different stimulus conditions with their corresponding MDT or AC values. This analysis uses the six contrast levels tested for each voxel (two per stimulus type) to determine, for each voxel, whether either a cone-contrast metric (AC) or threshold-scaled metric (MDT) is a better predictor, accounting for more of the variance in the fMRI signal. Results are shown in Fig. 7. The figure shows that the AC metric (shown by the red scale) covaried more with the BOLD response than the threshold-scaled (MDT) metric (shown by the green scale) in areas V1 and parts of V2. These data therefore suggest that equivalent BOLD responses are better predicted from stimuli of equivalent contrast rather than equivalent MDT. In Fig. 7 it is clear that the better predictive power of the cone-contrast metric was found in the more peripheral regions (red colouring); it was less predictive near the fovea (grey colouring). This may reflect a relative loss of colour sensitivity away from the fovea, as has been documented psychophysically (Mullen, 1991; Mullen *et al.*, 2005), and this is investigated in the following section.

Dependence on eccentricity

In Fig. 8 we aim to identify any dependence on eccentricity of the relative responses to chromatic and Ach stimuli. We have plotted the individual data for responses in V1 as a function of eccentricity for the higher-contrast stimuli, matched in MDT, as these are more reliable for exploring across eccentricity. The data show that the very robust response to BY stimuli over the RG and Ach found in the MDT condition (Fig. 6) was maintained across eccentricity. The results also show that the BY response across eccentricity had a similar form to that for the Ach stimuli (no significant difference in slopes across subjects; $t = -0.35$, $P > 0.7$); however, the RG response declined in relation to the other two, and the gap between RG and BY stimuli increased with eccentricity. The slope of RG was significantly different from both Ach ($t = 3.90$, $P = 0.003$) and BY ($t = 3.00$, $P = 0.019$) in our subjects. A similar result, in which RG shows a differentially greater loss across eccentricity, has recently been reported using a different, multifocal fMRI approach (Vanni *et al.*, 2006). Furthermore, a steeper loss of RG than BY or Ach contrast sensitivity across the visual field is also found psychophysically (Mullen, 1991; Mullen & Kingdom, 2002).

Discussion

For our experiments, we identified eight visual areas or regions in the human cortex, of which six areas were directly localized from retinotopic mapping using a phase-encoded method (Engel *et al.*, 1994; Sereno *et al.*, 1995; Dumoulin *et al.*, 2003), area hMT+ was localized using a flickering stimulus (Dumoulin *et al.*, 2000), and a further region (termed VO) extending anterior to V4 was identified using the experimental stimuli. The purpose of our experiments was to make a quantitative comparison of the responses of the two colour systems, S-cone-opponent and L/M-cone-opponent, and the Ach system within each visual area, using a design in which three response types were measured within a single scan.

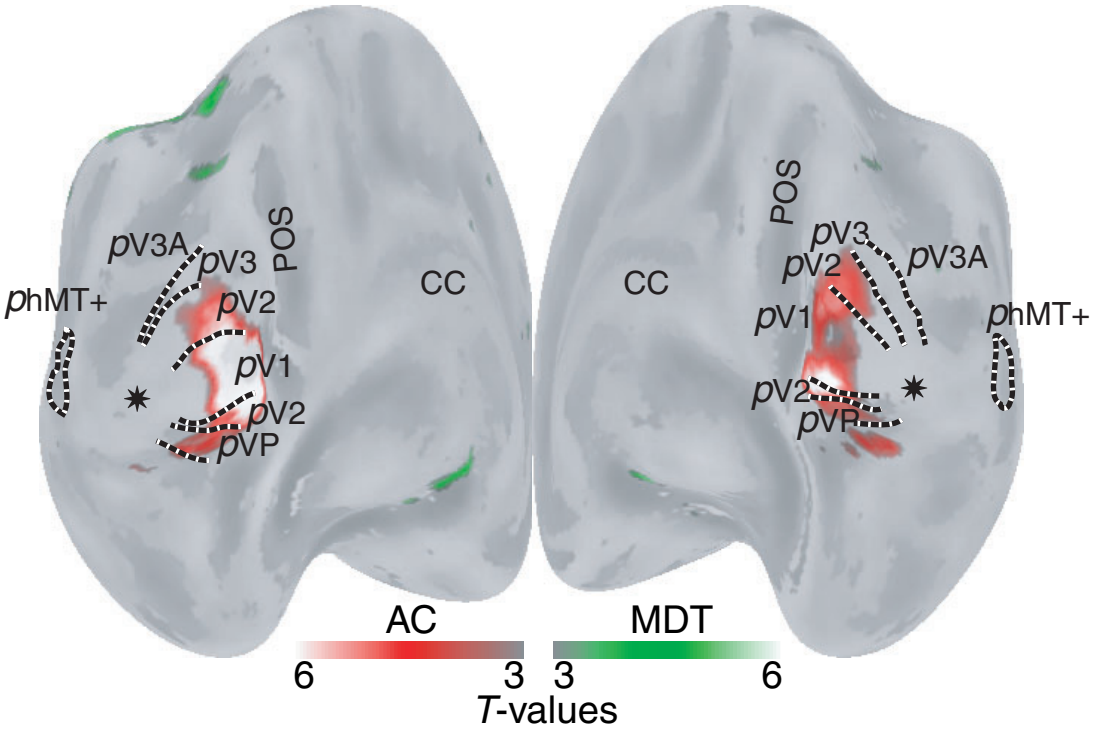

FIG. 7. Average *t*-statistical map ($n = 8$) showing regions that covary with the AC of the stimuli (in red), and regions that covary with the stimulus contrast expressed in MDT (in green). Results are displayed on average unfolded cortical surfaces with the oblique medial views of the left and right hemisphere shown on the left and right, respectively, and are the same views with the same annotations as in Fig. 3.

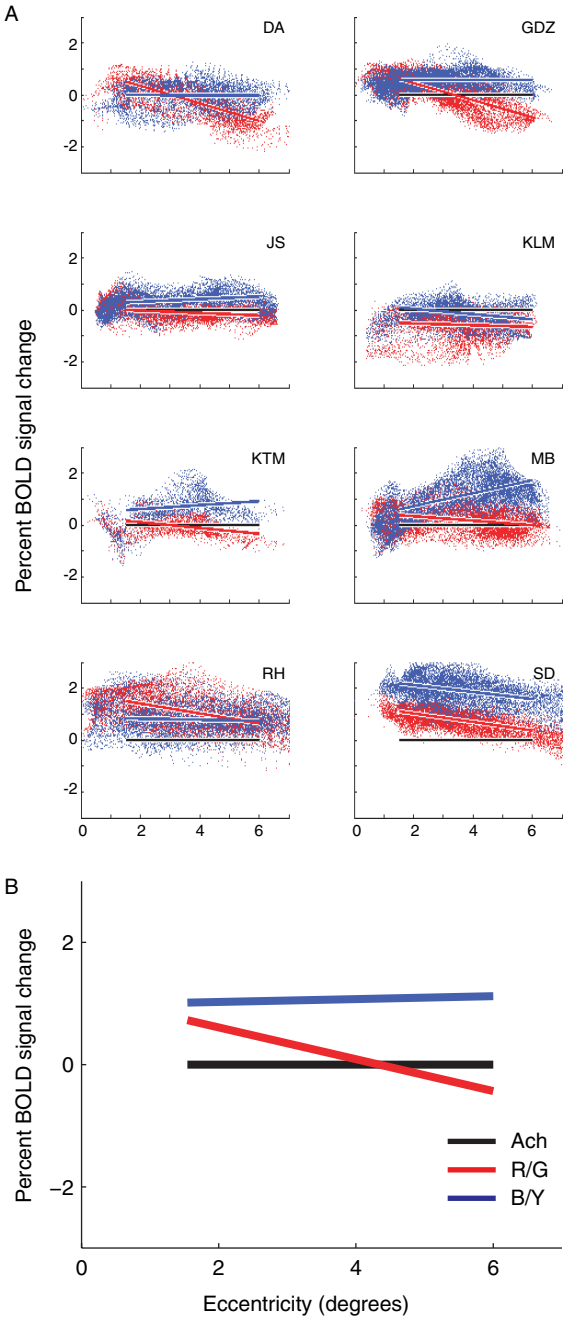

FIG. 8. Percentage BOLD signal change in area V1 is plotted as a function of eccentricity for (A) individual data on the eight subjects and (B) the average data for the condition in which stimuli are matched in MDT. The data are colour-coded according to the different stimulus conditions. Straight lines are fitted to the data. This fit is done between 1.5° and 6° eccentricity because this is the most reliable data range (stimulus size is 8° by 6° radius). Data for subjects RH and SD extend beyond 6° because the retinotopic maps were defined with a larger stimulus (radius 16°) than for the other subjects. The parameters of the fits (slope and intercept) for the individual subjects are averaged to create the fits shown in panel B. The data show that the relative responses to the different stimuli depend on eccentricity.

Contrast metrics

We considered two possible metrics as the basis for the comparison of colour and Ach responses, illustrated in Fig. 1. The first, termed AC, expresses stimulus contrast, whether chromatic or Ach, in terms of cone contrast at the level of the cone receptors. With this metric, stimuli have different visibilities as the L/M- and S-cone-opponent systems and the Ach system all have different visual thresholds. The second metric expresses stimulus contrast in terms of multiples of the stimulus detection threshold (MDT), and so equates stimuli at a higher postreceptoral level after sensitivity differences have occurred, and approximately equates in terms of stimulus visibility. Our results (Fig. 7) show that, particularly for the early visual areas of V1 and V2, the cone-contrast metric is a better predictor of the fMRI response than a metric that scales by detection threshold to lessen or remove stimulus visibility differences. Neither metric was better in the remaining areas. This effect, that overall visibility is a poor predictor of BOLD response, is demonstrated clearly by the BY stimulus. For example, when the BY and RG stimuli were presented at similar cone contrasts, the BY stimulus (at only 5× its detection threshold) was poorly visible but the RG stimulus (at 31× its detection threshold) was highly visible (Fig. 1), yet both stimuli produced similar and robust fMRI responses (Fig. 5). Correspondingly, when stimuli were equated in MDT, so compensating for differences in visual sensitivity, the BY response was dominant and was significantly greater than the RG response in most cortical areas (V1, V2, V3, VP, V4). This BY dominance most probably occurs because of the high cone contrast required to match BY stimuli to the others in terms of their detection thresholds, reflecting the influence of contrast rather than visibility in determining the BOLD response.

Our result, that psychophysical threshold scaling is not manifest in the BOLD responses, differs from two previous investigations using similar stimuli that found consistently lower relative responses to S-cone-isolating stimuli (BY), which so are more in line with human visual thresholds (Engel *et al*., 1997a; Liu & Wandell, 2005). For our stimuli equated in cone contrast, some ordering of the BOLD response in relation to threshold was apparent in the VOI results for areas V1 and VO (Fig. 5), as these areas have a significantly higher response to RG than to Ach stimuli, but this effect was clearly not consistent for the BY stimuli as the poor contrast sensitivity of human vision to BY was not reflected in the fMRI responses. The very robust fMRI response to our BY stimuli was unlikely to be due to luminance artifacts as these would be an effective stimulus for MT, when in fact the response of hMT+ to the BY stimulus was very weak. By the same token, the response of the colour-sensitive region VO to any luminance artifact would be expected to be low, when in fact VO responded well to the BY stimulus. Our methods, stimuli and psychophysical thresholds were generally similar to the previous study (Liu & Wandell, 2005) that reported weaker BY responses, but with two exceptions. First, because attention is known to modulate fMRI responses in both V1 and extrastriate areas (Somers *et al*., 1999), we used a contrast-discrimination task that focused the subjects' attention on the stimuli and controlled for attention levels across the three stimulus types, whereas Liu & Wandell (2005) used a fixation mark task designed to direct attention away from the test stimulus. It is possible that focusing attention on the stimuli acts to raise the response to the less visible ones, typically the BY stimuli at equivalent cone contrasts, and may allow a greater contribution from the nonfoveal regions that are responding only to the test stimulus and not to the fixation stimulus. Second, our experimental design was optimized for relative comparisons between responses to the three stimulus types (RG, BY and Ach) as all three stimuli were presented within each scan. Liu & Wandell (2005), on the other hand, presented stimuli of only one type (colour and contrast level) in each scan, as they were measuring contrast response functions, and so comparisons across the condition of colour are made across different scans and might be affected by varying attention or adaptation. It is not clear which, if any, of these differences account for why we found a much more robust

response to S-cone stimuli. Moreover, Liu & Wandell (2005) found that their correspondence between relative threshold scaling and BOLD disappeared at higher temporal frequencies.

The robust response we found for the S-cone-opponent system is interesting in view of the very sparse population of S-cone-sensitive neurons present in primate subcortical pathways, and suggests a relative enhancement of the S-cone colour response at the cortical level. Differential contrast gains for S-cone responses have been suggested by single-cell primate neurophysiology (De Valois *et al*., 2000; Solomon & Lennie, 2005) but remain controversial (Johnson *et al*., 2004). Furthermore, enhancement of the S-cone response might also be manifest at the behavioural level. So far, we lack any detailed knowledge of the differential psychophysical suprathreshold contrast gains of the three mechanisms. For example, as suggested by Georgeson & Sullivan (1975) in the context of spatial frequency, some form of contrast normalization may be implemented at the level of the cortex to boost S-cone signals, so compensating for the poor psychophysical thresholds by reducing the perceptual differences between RG, BY and Ach stimuli at higher suprathreshold contrasts. Viewing of our stimuli matched in MDT (lower row of Fig. 1) suggests that threshold scaling is a reasonable means of matching stimulus visibility, although this issue requires further investigation psychophysically. Lastly, although we have shown that cone contrast predicts the BOLD response better than a threshold-scaled contrast metric, particularly in V1, it is quite possible that a different metric or combination of metrics might do a better job than either. The relationship between the mass fMRI response (averaged across brain area in the VOI analysis) and threshold detection, which replies on a small number of highly sensitive neurons, is likely to be complex and difficult to predict.

Relative S-cone-opponent, L/M-cone-opponent and Ach responses across different cortical areas

The early visual areas, V1, V2, V3, VP and V4, all show robust responses to colour. For stimuli matched in cone contrast, all these areas, with the exception of V1, showed similar responses to chromatic and Ach stimuli, and all responded as well to BY as to RG stimuli. Although V1 showed a preference for chromatic over Ach stimuli in the surface plots (Figs 3 and 4), the colour preference, notably for RG, tended to diminish with increasing eccentricity (Fig. 8). Hence in the VOI analyses, which average across all regions of the visual field tested including the more peripheral and less colour-sensitive regions, a more moderated response of V1 to chromatic stimuli was found (Figs 5 and 6).

A response of V1 to colour has been well established in previous fMRI studies (McKeefry & Zeki, 1997; Hadjikhani *et al*., 1998; Bartels & Zeki, 2000; Wade *et al*., 2002; Brewer *et al*., 2005), but only a few have made quantitative comparisons between RG, BY and Ach responses (Engel *et al*., 1997a; Liu & Wandell, 2005). As discussed above, our results differ from these latter two studies in terms of the level of S-cone response that we found, especially apparent for stimuli scaled for visual threshold when all areas except hMT+ responded significantly more strongly to S-cone stimuli. The robust response of V1 to RG colour is reflected in primate neurophysiological data showing that, when a cone-contrast metric is employed, at least 50% of neurons in macaque V1 are responsive to RG colour contrast (Johnson *et al*., 2001, 2004), but the robust S-cone response is surprising in view of the low numbers of cortical neurons responsive to S-cone stimulation. We note that our stimuli are of a relatively low spatial and temporal frequency (0.5 c.p.d., 2 Hz), chosen because these parameters favour chromatic sensitivity psychophysically (Mullen, 1985). It is quite likely that the colour response of these areas would be reduced relative to the Ach at higher spatial frequencies. Evidence also suggests that raising temporal frequency (e.g. to 10 Hz) selectively reduces the S-cone response over the that of L/M in most cortical areas (Liu & Wandell, 2005).

Our results show that human V4 has no significant overall preference for colour, even though the stimuli we used were selected to be optimal for chromatic activation. This result supports primate data, obtained using different techniques, that also suggest that V4 has robust responses to colour but is without overall colour preferences (Heywood *et al*., 1992; Tootell *et al*., 2004). On the other hand, we found a region anterior to V4 that had a significant preference for colour over Ach stimuli, the preference being consistent over the two contrast metrics. We used the term VO for this area based on its anatomical location, identified from its response to the experimental stimuli as shown in the stereotaxic representation of Fig. 3. In general this cortical location has been found to be particularly responsive to colour (Zeki *et al*., 1991; Hadjikhani *et al*., 1998; Brewer *et al*., 2005) but has been named differently by different researchers, and its retinotopic details are still controversial (Hadjikhani *et al*., 1998; Wade *et al*., 2002; Brewer *et al*., 2005; Liu & Wandell, 2005; Wandell *et al*., 2005), although some have argued that VO and V4 represent a single brain area (Zeki *et al*., 1998). We found that region VO showed a consistent and significant preference for the colour stimuli and responded as well to RG as to BY. The responses of VO clearly differed from those of V4, which had no significant preference for colour under either contrast metric, and so our results provide key evidence for a functional distinction between areas V4 and VO, supporting their separate identities. Overall, our results support the view that human brain areas within the ventral stream correspond to colour and Ach contrast, with a strong parvocellular and koniocellular input to these regions. A colour specialization, defined as a significantly stronger response to chromatic than to Ach stimuli, only emerge in VO, although this area still retained a strong response to Ach contrast.

Our results identify two visual areas, V3A and hMT+, that have significantly greater responses to the Ach than to the chromatic stimuli, consistent across the two contrast metrics used. In particular, hMT+ stands out for its strong differential response to Ach stimuli over both chromatic stimuli (Figs 5 and 6). Although it has been reported previously that hMT+ responds to both S-cone- and L/M-cone-opponent modulations (Wandell *et al*., 1999; Liu & Wandell, 2005), our results differ from those of Liu & Wandell (2005), who found that hMT+ had similar responses to RG and Ach contrast for stimuli presented at equivalent cone contrasts and at a similar temporal frequency to ours. Our data also show that V3A and hMT+ had a similar pattern of results, with a significantly greater response to Ach stimuli under most conditions (Table 4). This suggests that these two areas are functionally related, and supports a similar conclusion made by Liu & Wandell (2005). Previous studies have suggested that human V3A, like hMT+, is relatively motion-selective (Tootell *et al*., 1997) and has an enhanced response to flicker (Liu & Wandell, 2005). This contrasts with macaque data showing V3 to be more motion-selective than V3A and supports the idea of a reversal of function between V3 and V3A for macaque and human brains (Tootell *et al*., 1997). Our data suggest that there is a relatively strong magnocellular input to human V3A and hMT+ and links these two areas into a dorsal pathway that has very poor sensitivity to both L/M- and S-cone-opponent modulation. The small S-cone response of hMT+ that we found may be mediated by an S-cone contribution to magnocellular neurons as reported in macaque (Chatterjee & Callaway, 2002), or possibly by a direct koniocellular input from the LGN to MT also as

found in macaque (Sincich *et al*., 2004), although we note that koniocellular cells are a heterogeneous group not exclusively driven by S-cones.

Based on visual field mapping, Wandell *et al*. (2005) and Brewer *et al*. (2005) have proposed that the different retinotopic visual areas in human brain are organized into clusters with each cluster sharing a confluent fovea and a semicircular eccentricity map. Four of the clusters so far proposed include a posterior cluster (V1, V2, V3 and hV4), a cluster around V3A and V3B, a lateral cluster around hMT+ and a ventral cluster, not yet mapped in detail, that includes VO and further retinotopic representations believed to lie nearby. While the accuracy of the mapping data is still developing, the putative grouping of the different visual areas would be greatly strengthened by a functional as well as an anatomical link. Our data tend to support the functional grouping of V1, V2, V3 and hV4 as we found that these areas do not show consistent preferences for chromatic or Ach stimuli, responding similarly to all stimuli when presented at similar cone contrasts. Our data suggest that VO is functionally distinct from hV4, based on its significant preference for chromatic stimuli under both contrast metrics, and adds quantitative evidence in support of the functional separation of a VO cluster suggested by Wandell *et al*. (2005) and Brewer *et al*. (2005). Our data also support hMT+ as a distinct area based on its significant preference for Ach stimuli, and indicate a functional link with area V3A within the dorsal pathway despite its disparate location.

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Abbreviations

AC, absolute cone contrast; Ach, achromatic; 2AFC, 2-alternateforced choice; BOLD, blood oxygen level-dependent; BY, blue–yellow; Col, the two colour stimuli; c.p.d., cycles per degree; DO, dorsal occipital; fMRI, functional magnetic resonance imaging; h (as a neuroanatomical prefix), human; hMT+, human medial temporal areas; L/M-cone, long- and meduim-wavelength-absorbing cone; LO, lateral occipital; MDT, multiples of detection threshold; MO, medial occipital cortex; MT, medial temporal cortex; RG, red–green; S-cone, short-wavelength-absorbing cone; V, visual area; VO, ventral occipital cortex; VOI, volume of interest; VP, ventral posterior cortex; +, including related visual areas (as part of a neuroanatomical abbreviation).

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