An fMRI Version of the Farnsworth–Munsell 100-Hue Test Reveals Multiple Color-selective Areas in Human Ventral Occipitotemporal Cortex

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Studies of patients with cerebral achromatopsia have suggested that ventral occipitotemporal cortex is important for color perception. We created a functional magnetic resonance imaging (fMRI) version of a clinical test commonly used to assess achromatopsia, the Farnsworth–Munsell 100-Hue test. The test required normal subjects to use color information in the visual stimulus to perform a color sequencing task. A modification of the test requiring ordering by luminance was used as a control task. Subjects were also imaged as they passively viewed colored stimuli. A limited number of areas responded more to chromatic than achromatic stimulation, including primary visual cortex. Most color-selective activity was concentrated in ventral occipitotemporal cortex. Several areas in ventral cortex were identified. The most posterior, located in posterior fusiform gyrus, corresponded to the area activated by passive viewing of colored stimuli. More anterior and medial color-selective areas were located in the collateral sulcus and fusiform gyrus. These more anterior areas were not identified in previous imaging studies which used passive viewing of colored stimuli, and were most active in our study when visual color information was behaviorally relevant, suggesting that attention influences activity in color-selective areas. The fMRI version of the Farnsworth–Munsell test may be useful in the study of achromatopsia.

Introduction

Studies of cerebral achromats – humans who have lost the ability to perceive color as a result of brain damage – have suggested that ventral occipitotemporal cortex plays a crucial role in the processing of color information (Meadows, 1974; Damasio *et al.*, 1980; Zeki, 1990).

The organization of color processing areas in ventral cortex remains a subject of controversy. A number of functional imaging studies have suggested that color processing is found primarily in a single posterior ventral focus (Sakai *et al.*, 1995; Kleinschmidt *et al.*, 1996; Clark *et al.*, 1997; McKeefry and Zeki, 1997) which has been labeled as a human homologue of monkey V4 (Zeki *et al.*, 1991) or as a uniquely human area V8 (Hadjikhani *et al.*, 1998). While most previous studies have used passive viewing of colored stimuli, two studies that used simple color discriminations found more extensive color-selective activity encompassing ventral cortex and a number of other brain regions (Corbetta *et al.*, 1991; Gulyas and Roland, 1994).

One difficulty in interpreting these conflicting results is that previous studies have used passive viewing of colored stimuli or simple color discriminations to determine color-selective areas. Yet patients with cerebral achromatopsia show sensitivity to chromatic differences (such as detection of chromatic gratings) perhaps based on color-opponent responses in primary visual cortex (Victor *et al.*, 1989; Heywood *et al.*, 1996). The central deficit of cerebral achromatopsia is the loss of the conscious perception of color and the accompanying ability to use color information in the visual stimulus to make behavioral choices. Therefore, there is a mismatch between the tasks used in previous imaging studies (passive viewing of colors or simple color discriminations) and the deficits reported in cerebral achromatopsia.

We created a functional magnetic resonance imaging (fMRI) adaptation of a clinical test commonly used to assess cerebral achromatopsia, the Farnsworth–Munsell 100-Hue test (Farnsworth, 1957). Because the test requires the use of color information to make perceptual decisions about the sequencing of colors, it is closely linked to the perceptual deficits reported by cerebral achromats, who perform at chance levels on the 100-Hue test (Victor *et al.*, 1989; Heywood, *et al.*, 1996). The similarity of the clinical test and our fMRI version means that it may be useful in studying both the organization of color-selective areas in normal subjects and the results of damage to these areas in patients with cerebral achromatopsia.

Materials and Methods

Subjects

Twelve human subjects (five male, seven female, average age 27.7 years) underwent a complete physical examination, including color-vision screening with the full version of the Ishihara plates (Ishihara, 1971) before fMRI was performed. Within each MRI session, subjects performed as many as three separate experiments: an adaptation of the clinical 100-Hue test (n = 12); passive viewing of the 100-Hue stimuli (n = 10); and passive viewing of Mondrian stimuli (n = 4).

Farnsworth–Munsell 100-Hue Clinical Test and fMRI Adaptation

In the 100-Hue clinical test (GretagMacbeth, New Windsor, NY) 87 calibrated color caps are placed in a regular color sequence by the subject. Using the CIE color co-ordinates of the caps obtained from the manufacturer, a graphics board (Cambridge Research Systems, Cambridge, UK) was programmed to backproject the colors onto a Lucite screen with a video projector. In order to prevent luminance difference artifacts (Heywood *et al.*, 1992) the luminance of each test color for each subject was matched in a flicker photometry session (Rushton and Baker, 1964) performed outside the scanner. Using the same projection system and viewing distance as was used during scanning, subjects fixated while viewing an annulus located at the stimulus eccentricity which alternated at 15 Hz between the test color and a uniform gray of luminance 53 cd/m^2. Subjects adjusted the luminance of each test color to minimize the perceived flicker.

Each MR scan series contained six 21 s blocks of visual stimulation alternating with equal-length fixation periods (Fig. 1*A*). Each block consisted of seven 2.5 s trials, separated by intertrial intervals of 0.5 s. Only chromatic or achromatic stimuli were presented in each block. The block order (chromatic or achromatic first) was counterbalanced across scan series. The stimulus in both chromatic and achromatic trials consisted of five wedges arrayed around a central fixation bar, extending from one to four degrees of eccentricity. This range was chosen because there are no S-cones in central fovea, and cone density decreases dramatically in the periphery (Curcio *et al.*, 1990). During chromatic trials, the wedges at the 10 o'clock and 2 o'clock positions contained two anchor hues, a randomly selected pair of colors eight caps apart in the 100-Hue color series. Subjects decided if the colors in the intervening

wedges formed an orderly sequence, pressing a right-handed button if they did and a left-handed button if they did not. During achromatic trials, wedges of different luminance were presented and subjects responded by button press to the presence of a regular luminance sequence. The average luminance of the achromatic wedges was equal to the chromatic wedge luminance of 53 cd/m^2, and all wedges were brighter than the background (10 cd/m^2). Reaction time (RT) and percent correct data were recorded and subjects were instructed to keep their eyes on the fixation bar at all times. Prior to scanning, subjects performed the luminance-matching procedure and were trained on both tasks to a criterion level of 80% correct.

Passive Viewing Experiments

During the 100-Hue passive viewing experiment, subjects viewed the chromatic and achromatic 100-Hue stimuli but pressed both response buttons at the onset of each trial. During the Mondrian experiment, the methods described in Zeki *et al.* (1991) were followed as closely as possible, including instructions to make regular eye movements during stimulus presentation. A Land color Mondrian adapted from Hubel (1988) was presented, alternating with fixation and a luminance-matched achromatic Mondrian.

MRI Procedures

Anatomical MR scans were screened by the NIH Clinical Center Department of Radiology in accordance with the NIMH human subjects committee. A high-resolution SPGR scan was taken preceding the collection of 8–12 functional scan series. All functional images were then aligned to the first functional volume using AIR v. 3.08 (Woods, 1998; Woods *et al.*, 1998). Two subjects with movement artifacts not correctable by AIR were discarded from the study. Eighty-eight echo-planar images were collected in each scan series using a 1.5 T scanner (General Electric, Milwaukee, WI) with a repetition time (*TR*) of 3000 ms, an echo time (*TE*) of 40 ms, and in-plane resolution of 3.75 × 3.75 mm. Depending on the geometry of each subject's brain, from 21 to 25 axial slices with a thickness of 4 or 5 mm were collected to provide whole brain coverage.

Data Analysis

Multiple regression was used to detect stimulus-related changes in the MR signal (Rencher, 1995; Worsley *et al.*, 1997; Haxby *et al.*, 1999). Two regressors of interest were used: the first revealed differences between stimulation and fixation, while the second revealed differences between chromatic and achromatic stimulation. FIDAP software (Haxby, 1998) determined the statistical significance of the proportion of variance accounted for by all regressors of interest combined (the experimental effect) and for each regressor of interest individually. Figure 1*B*,*E* illustrates sample MR time series (blue lines) and best-fit combinations of both regressors of interest (red lines). A two-stage process was used to find color-selective regions. First, all brain voxels were examined to find voxels showing an experimental effect, using a rigorous threshold of $z > 4.416$ ($P < 10^{-5}$ per voxel) to correct for multiple comparisons. The few voxels which passed this test underwent a less stringent thresholding by the second regressor of interest (which measured color-selectivity) at $z > 1.6$ ($P < 0.05$ per voxel).

Results were interpolated and overlaid on each subject's anatomical scan before conversion to the standardized space of Talairach and Tournoux (1988) using AFNI v. 2.20 (Cox, 1996, 1998). For descriptive purposes, adjacent voxels that passed both thresholds were grouped into clusters in order to create average MR time series and calculate the center-of-mass of active regions. The location of active regions are reported in Talaraich coordinates as the distance in mm from the anterior commissure in the form (*x*,*y*,*z*) where the *x*-axis is left-to-right, the *y*-axis is posterior-to-anterior and the *z*-axis is inferior-to-superior. To make average activation maps, chi-square maps for both regressors of interest were created for each subject, blurred with a spatial Gaussian filter of root mean square width 3 mm, averaged, and overlaid on averaged standardized anatomical scans.

Results

Behavioral Data

Subjects' accuracy and RT were equivalent for the chromatic and achromatic versions of the task [chromatic: 82 ± 8% correct (SD), RT 1640 ± 170 ms; achromatic: 85 ± 8% correct (SD), RT 1650 ± 160 ms].

Single Subject 100-Hue Results

Visually responsive regions in occipital, temporal, parietal and frontal cortex showed greater response during stimulation blocks than during fixation. However, most of the brain regions which showed greater activity during stimulation blocks than during fixation did not differentiate between chromatic and achromatic blocks. The few areas that did show greater activation to chromatic than achromatic stimulation were concentrated in ventral occipitotemporal cortex. No areas showed consistently greater activation to achromatic stimuli.

Typical results from a single subject are shown in Figure 1. A group of dorsal occipital voxels responded with increased MR signal intensity during stimulation blocks and a return to baseline during fixation, with an average signal change of 1.5% (Fig. 1*B*). While many dorsal voxels showed highly significant intensity changes in response to visual stimulation (Fig. 1*C*, right panel, $z = 26$ mm) none of these voxels showed a significant response difference between chromatic and achromatic blocks (Fig. 1*D*, right panel).

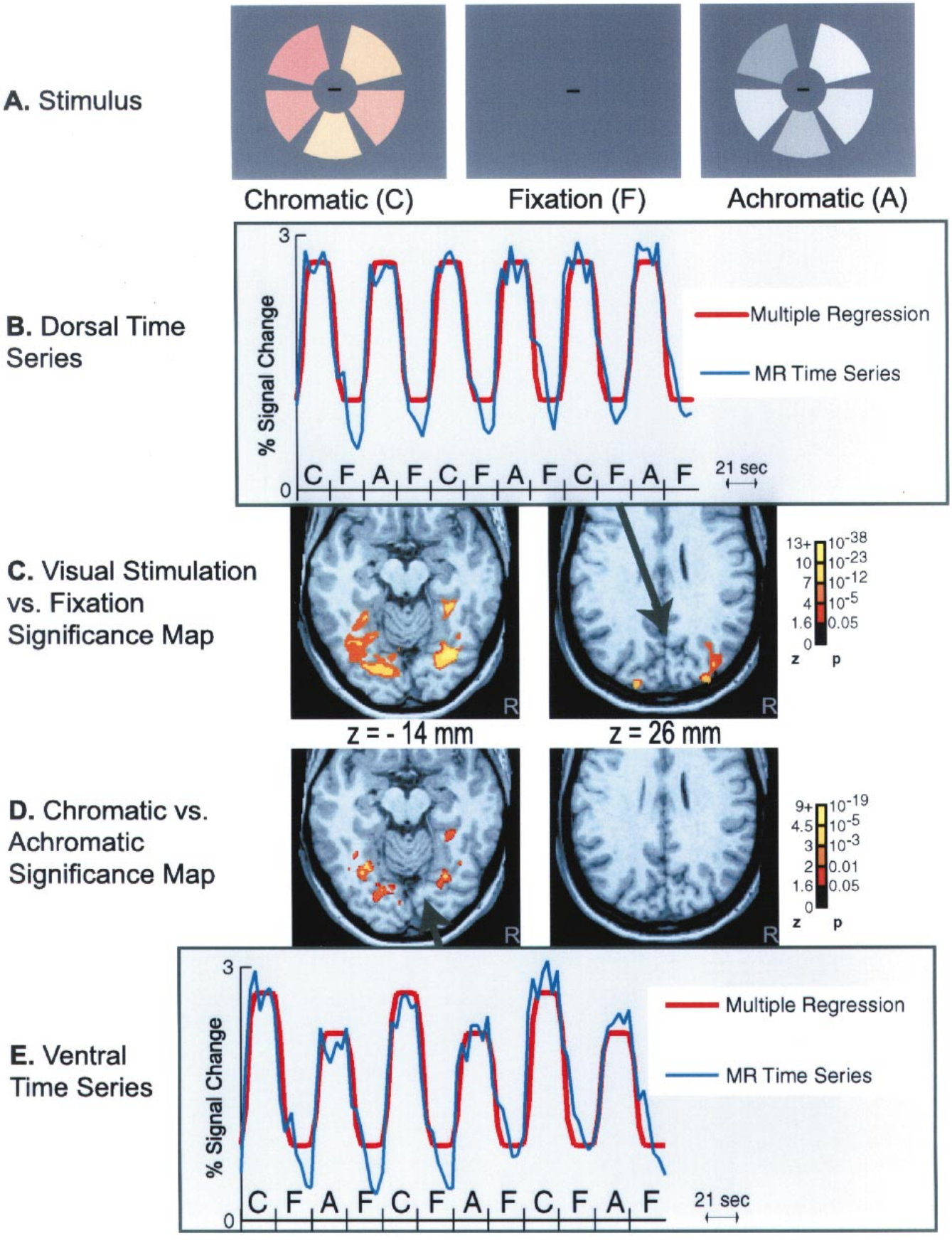
In contrast to this non-selective response, a region in ventral occipitotemporal cortex did differentiate between chromatic and achromatic stimulation. Figure 1*C* (left panel, $z = -14$ mm) illustrates bilateral ventral voxels that responded to visual stimulation. Many of these ventral voxels significantly preferred chromatic to achromatic stimulation (Fig. 1*D*, left panel). The average time series from these voxels (Fig. 1*E*) illustrates that the response to stimulation was strong (average signal change of 1.5%) but the response was significantly greater to chromatic than achromatic blocks (1.9% versus 1.0% respectively, $P < 0.0001$).

The anatomical distribution of color-selective activity was not uniform in ventral cortex. Instead, it was grouped into distinct areas along the collateral sulcus in the lingual and fusiform gyri. In an individual subject, cluster analysis revealed three distinct color-selective regions in left and right ventral cortex (Fig. 2*A*). Color-selective activity was also observed in calcarine cortex, dorsomedial occipital cortex and in the intraparietal sulcus.

Average 100-Hue Results

There was a similar organization of multiple color-selective areas in ventral cortex in 12 subjects performing the 100-Hue task (Fig. 2*B*). Four local maxima were found in the average activation

Figure 1. Visual stimulus and fMRI activation in a single subject during performance of the Farnsworth–Munsell 100-Hue test. (*A*) Within each scan series, the subject alternated between blocks of chromatic or achromatic discrimination trials and fixation. (*B*) The average MR time series (blue line) from dorsal occipital areas showing a significant response to stimulation with best-fit output of multiple regression (red line) illustrating response during chromatic blocks, achromatic blocks and fixation (labeled on *x*-axis). (*C*) Areas showing a significant response to chromatic or achromatic stimulation vs. fixation ($P < 0.05$) in ventral occipital cortex (left slice) and dorsal occipital cortex (right slice). (*D*) Areas showing a significant difference in response to chromatic versus achromatic stimulation ($P < 0.05$) in ventral and dorsal occipital cortex. (*E*) The average time series from ventral areas with a significant response difference to chromatic versus achromatic stimulation ($P < 0.05$). In (*C*) and (*D*), only clustered voxels (spatial nearest-neighbor cluster analysis) with experimental effect $P < 10^{-5}$ per voxel are pictured. Data shown are from case AL.


A. Stimulus
Chromatic (C)
Fixation (F)
Achromatic (A)
B. Dorsal Time Series
% Signal Change
3
0
Multiple Regression
MR Time Series
C F A F C F A F C F A F
21 sec
C. Visual Stimulation vs. Fixation Significance Map
13+ 10 7 4 1.6 0
10^{-38} 10^{-23} 10^{-12} 10^{-5} 0.05
z p
R
z = - 14 mm
z = 26 mm
D. Chromatic vs. Achromatic Significance Map
9+ 4.5 3 2 1.6 0
10^{-19} 10^{-5} 10^{-3} 0.01 0.05
z p
E. Ventral Time Series
% Signal Change
3
0
Multiple Regression
MR Time Series
C F A F C F A F C F A F
21 sec

map. The region with highest significance was found in right collateral sulcus/fusiform gyrus (30, –69, –9). The most anterior region (peak significance: –19, –46, –7) was located in left mid-fusiform gyrus. A second color-selective region in left ventral cortex was located more posteriorly in collateral sulcus/fusiform gyrus (–28, –58, –12). The most posterior region (–22, –80, –10) was located in posterior fusiform gyrus and the banks of the collateral sulcus. The preponderance of average color-selective activity in left ventral cortex reflected laterality in the individual subject maps. While all subjects displayed bilateral ventral color-selectivity, the activity was stronger in the left ventral cortex in 9 out of 12 subjects. On average, subjects displayed 24 ± 10% (SEM, $P < 0.01$) fewer occipitotemporal color-selective voxels in right ventral cortex than left ventral cortex. Color-selectivity was also observed in the average map in calcarine cortex. Across subjects, the largest concentration of color-selective activity was found in ventral cortex (51 ± 3% SEM of all color-selective voxels). Color-selective activity was also observed in all subjects in calcarine cortex (5 ± 1% of all color-selective voxels; average co-ordinates 1, –87, 1), left dorsolateral occipital (2 ± 1%; –28, –78, 19) and dorsomedial occipital cortex (7 ± 2%; 0, –81, 21). Color-selective activity was observed in seven subjects in left lateral frontal cortex (2 ± 1% of all color-selective activation; –36, 5, 32) and in nine subjects in superior parietal cortex (12 ± 3%; –2, –66, 47).

Passive Viewing Experiments

In order to compare the 100-Hue color-selective areas with those reported in other studies, we performed a second experiment as similar as possible to that of McKeefry and Zeki (1997). Four subjects viewed a colored Mondrian stimulus alternating with an achromatic luminance-matched version of the same Mondrian stimulus, with intervening rest periods. Multiple regression was used to find areas selective for the color Mondrian. In a third experiment, ten subjects passively viewed the 100-Hue stimuli.

Average activation maps from the four subjects who performed all three experiments are shown in Figure 3. Passive viewing of Mondrians (Fig. 3*C*) evoked color-selective activity in a posterior region in the left collateral sulcus/fusiform gyrus (–23, 81, –14) overlapping the most posterior location of color-selective activity during viewing of the 100-Hue stimulus (Fig. 3*A*,*B*). In addition to this posterior focus, the 100-Hue stimulus/task also evoked color-selective activity in more anterior color-selective areas. The most color-selective activity was always found during active performance of the 100-Hue task (Fig. 3*A*). Passive viewing of the 100-Hue stimuli (Fig. 3*B*) evoked color-selective activity in only 27 ± 7% (SEM, $P < 0.001$) as much ventral cortex as did active discrimination of the same stimuli. Passive viewing of the Mondrian stimulus evoked the least color-selective activity in ventral cortex, activating only 15 ± 11% (SEM, $P < 0.001$) as much cortex as the active 100-Hue task. As in the average activation map from 12 subjects, the average activation map from four subjects showed right ventral responses which were similar, but less extensive, than those in left ventral cortex. Only two of the four subjects showed right ventral activation to the Mondrian stimulus; bilateral activation was found in all subjects for the 100-Hue stimuli.

In order to examine the details of the ventral response, voxels in left ventral cortex were selected which showed both an overall experimental effect ($P < 10^{-5}$) and color-selectivity ($P < 0.05$) in any of the three experiments (Fig. 3, voxels within green dashed lines). Average MR time series were created to represent the anterior and posterior ventral responses in each experiment (Fig. 3 graph insets).

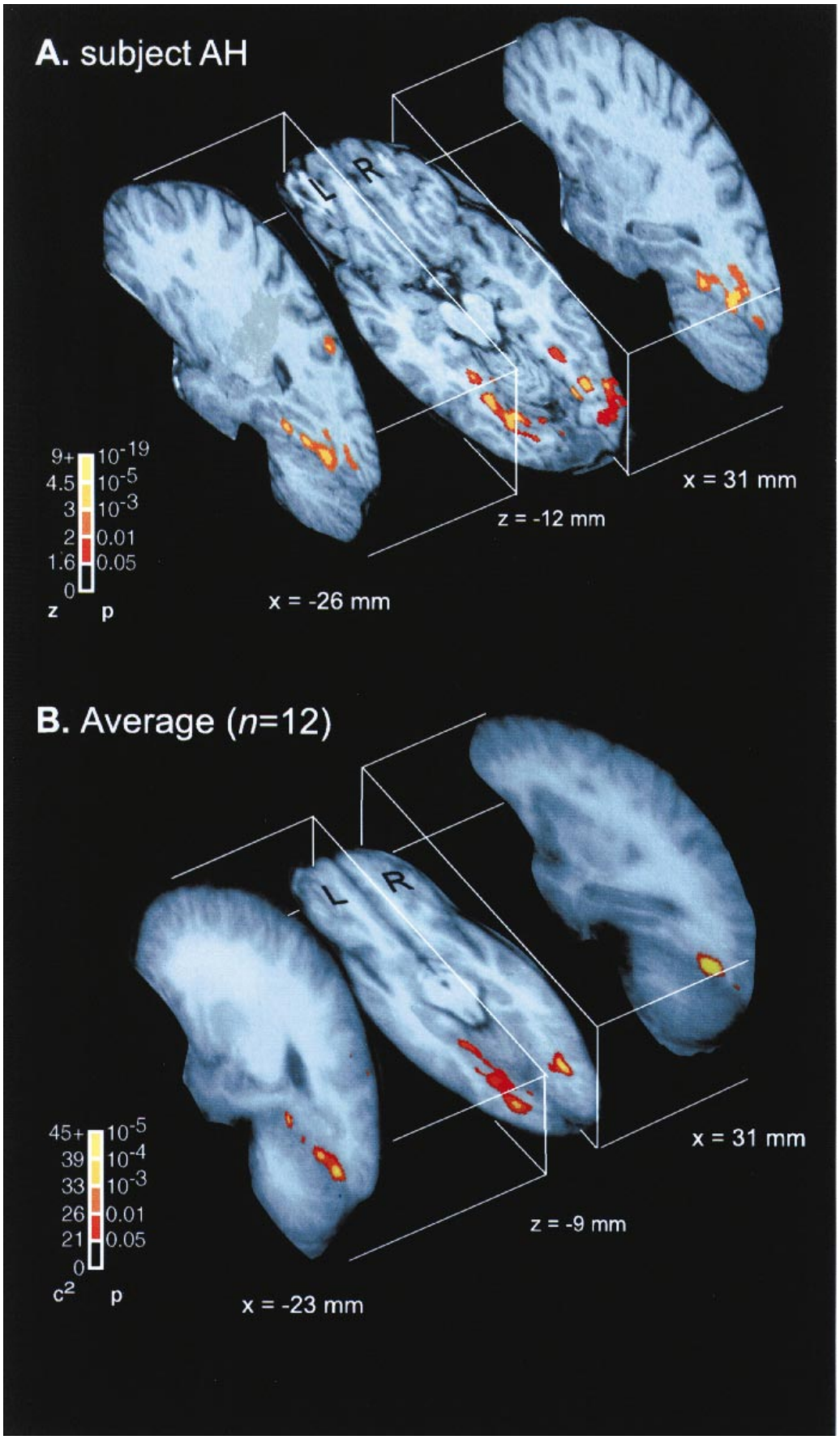
The magnitude of the response to stimulation was greatest during performance of the 100-Hue task as compared to both passive viewing of the 100-Hue stimuli ($P < 0.001$) and passive viewing of the Mondrian stimuli ($P < 0.001$). In all conditions, the response to chromatic stimuli was greater than the response to achromatic stimuli. No consistent difference in response between anterior and posterior areas was observed within each condition, so values are reported as the average of anterior and posterior responses. The active 100-Hue response was 2.5% for chromatic stimulation versus 1.6% for achromatic stimulation; the passive 100-Hue response was 1.9% versus 1.1%. The Mondrian stimulus evoked both a weak initial response at stimulus onset and a second response peak occurring immediately after offset of the Mondrian stimulus during the subsequent fixation period (Fig. 3*C* graph insets). Both the onset and offset responses were color selective, and we estimated their amplitude by constructing a reference waveform containing both onset and offset peaks. Using this reference waveform, the average response to the Mondrian condition was 1.0% for chromatic stimulation and 0.7% for achromatic stimulation. These results suggest that the failure of the Mondrian condition to reveal more color-selective areas was primarily a threshold effect due to the weak response evoked by the Mondrian stimulus. Averaging the response across voxels identified by the other conditions improved the signal-to-noise ratio of the hemodynamic response sufficiently to reveal significant responses to the Mondrian stimulus in anterior as well as posterior ventral areas. The improved signal-to-noise of the average response also revealed a response to stimulus offset not seen in individual voxel time series.

Discussion

Distribution of Color-selective Activity

Using a color-sequencing task, our study revealed a distributed network of color-selective areas in human cortex. Consistent with lesion studies that have demonstrated color deficits associated with damage to ventral cortex (Meadows, 1974; Damasio *et al.*, 1980; Zeki, 1990), most color-selective activation was concentrated in ventral occipitotemporal cortex. However, color-selective activity was not exclusive to ventral areas. Color-selectivity in calcarine cortex was observed in all subjects, consistent with electrophysiological evidence that some neurons in V1 show precise color-tuning and prefer colored stimuli (Gouras, 1972; Dow and Gouras, 1973; de Monasterio and Schein, 1982; Livingstone and Hubel, 1984) as well as previous imaging studies showing V1 color-selectivity (Gulyas and Roland, 1994; Kleinschmidt *et al.*, 1996; McKeefry and Zeki, 1997). Activation was found in some but not all subjects in left frontal cortex, as reported by McKeefry and Zeki (1997); dorsolateral

Figure 2. Color-selective activity in a single subject and in an average map from 12 subjects. (*A*) Regions with significant experimental effect ($P < 10^{-5}$ per voxel) and significantly greater chromatic than achromatic response ($P < 0.05$ per voxel) in an individual subject. (*B*) An average significance map from 12 subjects showing regions with significant experimental effect ($P < 10^{-5}$ per voxel) and color-selectivity ($P < 0.05$ per voxel) overlaid on an average anatomical image from the same subjects. In (*A*) and (*B*), color scale corresponds to degree of color-selectivity (significance of chromatic versus achromatic comparison) in each voxel.


A. subject AH
L
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9+
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z = -12 mm
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B. Average (n=12)
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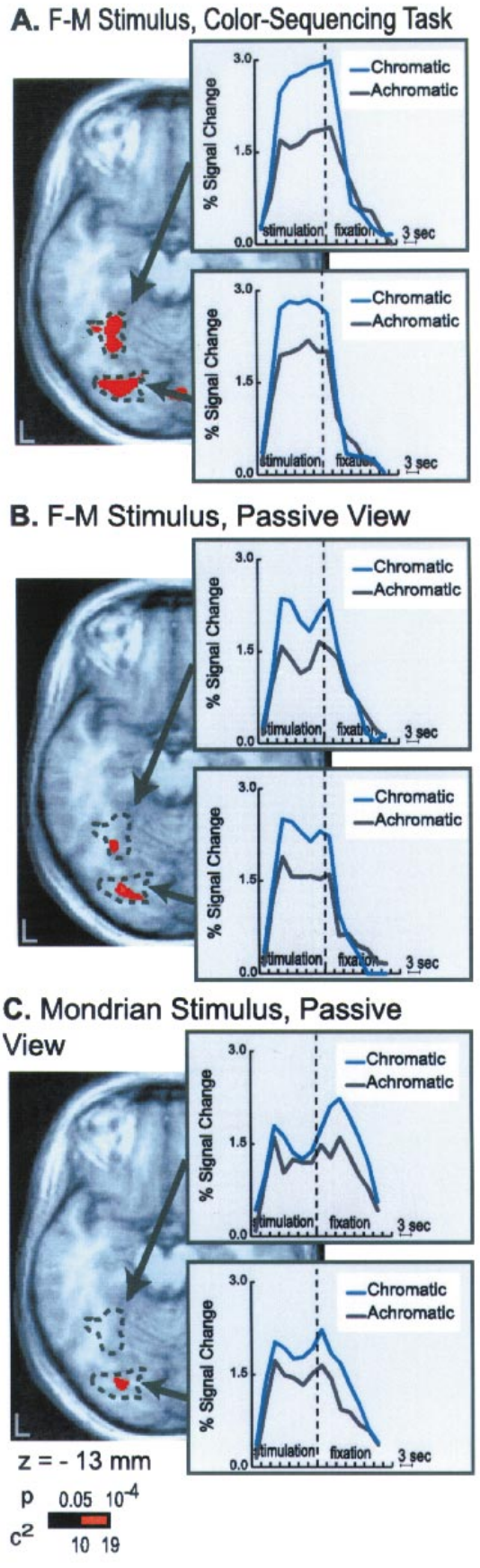

Figure 3. Ventral color-selective activity during three experiments, averaged across four subjects. Colored regions illustrate voxels showing both significant experimental effect ($P < 10^{-5}$) and significant color-selectivity ($P < 0.05$). (*A*) Color-selective activity during performance of the color-sequencing task while viewing the 100-Hue stimuli. (*B*) Color-selective activity during passive viewing of the 100-Hue stimuli. (*C*) Color-selective activity during passive viewing of the Mondrian stimuli. In (*A*), (*B*) and (*C*), color scale corresponds to degree of color-selectivity (significance of chromatic versus achromatic comparison) in each voxel. Anterior and posterior ventral regions which were active in any of the three experiments are shown outlined with green dashed lines. Inset graphs illustrate the average MR response from anterior regions (top graph) and posterior regions (bottom graph) during each experiment. Each inset graph shows the average response to a stimulation block and the following fixation period (labeled on *x*-axis) during chromatic stimulation (blue line) and achromatic stimulation (black line).

occipital cortex, consistent with the average results reported by Corbetta *et al.* (1991); and superior parietal lobe, as reported for average results of Gulyas and colleagues (Gulyas and Roland, 1994). In general, our color study is consistent with the notion that the processing of color is concentrated in ventral occipitotemporal cortex. While our results confirm that color-selective activity processing is not confined solely to ventral cortex (Corbetta *et al.*, 1991; Gulyas and Roland, 1994) they also do not suggest a globally distributed network of dozens of brain areas for processing color (Gulyas and Roland, 1994).

Ventral Color-selective Responses

This concentration of color-selectivity in ventral cortex is consistent with the strong link between ventral cortex damage to achromatopsia, and with previous imaging studies showing activation in occipitotemporal cortex. The location of our most posterior focus (–22, –80, –10) was within 15 mm of ventral foci reported in previous studies (Corbetta *et al.*, 1991; Allison *et al.*, 1993; Sakai *et al.*, 1995; Clark *et al.*, 1997; McKeefry and Zeki, 1997). However, our study also revealed more anterior ventral color-selective activity not reported in previous studies (with the exception of Gulyas and Roland, 1994).

One possible explanation for this more extensive ventral activity is that the complex color sequencing required by the 100-Hue task recruited more color-selective areas than the passive viewing of colors or simple color discriminations previously used. A second possibility is that the 100-Hue display is a more potent visual stimulus than that used in previous studies, because it presents a new set of hues every 3 s, in contrast with studies which used a static display (Sakai *et al.*, 1995; McKeefry and Zeki, 1997) and it contains large patches of color which cover the entire color spectrum, in contrast with studies which used a limited hue set (Zeki, 1990; Corbetta *et al.*, 1991; Gulyas and Roland, 1994; Clark *et al.*, 1997; McKeefry and Zeki, 1997).

Our replication of studies by Zeki *et al.* (1990; McKeefry and Zeki, 1997) using Mondrian stimuli provide evidence for both possibilities. More anterior areas responded poorly to the Mondrians but did respond to passive viewing of the 100-Hue stimuli, suggesting that the dynamic 100-Hue stimuli are an important contributor to the ventral response. However, these areas responded even more robustly during active performance of the 100-Hue task. More than three times as much ventral cortex was active during performance of the color-sequencing 100-Hue task as during passive viewing. This suggests that the cognitive operations needed to perform the color sequencing task, such as featural attention, are important in modulating activity in ventral color-selective areas, consistent with previous reports of dramatic effects of attention in extrastriate visual areas (Corbetta *et al.*, 1991; Beauchamp *et al.*, 1997; Wojciulik *et al.*, 1998). We conclude that the more extensive set of hues and

the dynamic presentation of the 100-Hue stimuli (relative to the static Mondrian) and the active use of color information required by the 100-Hue task (relative to passive viewing) contributed to the anterior color-selective activity reported in our study.

The fact that performance of a color-sequencing task activated multiple color-selective areas suggests that color processing may take place in a distributed fashion in ventral cortex (Felleman and Van Essen, 1991) rather than in a single color center. The existence of color areas more anterior to those previously reported may help resolve a discrepancy between imaging studies and monkey lesion studies. While Zeki *et al.* (1991) label the ventral center of color-selective activity as V4, lesions of monkey V4 produced only mild impairments that were not color-selective (Heywood *et al.*, 1992; De Weerd *et al.*, 1996) whereas more extensive lesions of ventral cortex produced impairments of color discrimination (Heywood *et al.*, 1995). We suggest that monkey ventral cortex may contain homologues of the multiple color-selective areas observed in human ventral occipitotemporal cortex. Removal of a single area (such as V4) might lead to small decreases in performance, whereas removal of a greater number of areas, as in Heywood *et al.* (1995), would result in severe disturbances of color perception.

The existence of multiple ventral color-selective areas may provide an explanation of the variation in residual chromatic abilities of achromats (Meadows, 1974). Perhaps patients who report less severe impairment of color vision have damage to only a subset of ventral color-selective areas. Future experiments, including imaging studies of achromats, may be able to determine how these multiple color-selective areas function in concert to process color information.

Notes

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