

ACTIVATION OF COLOR-SELECTIVE AREAS OF THE VISUAL CORTEX  
IN A BLIND SYNESTHETE

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ABSTRACT

Many areas of the visual cortex are activated when blind people are stimulated naturally through other sensory modalities (e.g., haptically; Sadato et al., 1996). While this extraneous activation of visual areas via other senses in normal blind people might have functional value (Kauffman et al., 2002; Lessard et al., 1998), it does not lead to conscious visual experiences. On the other hand, electrical stimulation of the primary visual cortex in the blind does produce illusory visual phosphenes (Brindley and Lewin, 1968). Here we provide the first evidence that high-level visual areas not only retain their specificity for particular visual characteristics in people who have been blind for long periods, but that activation of these areas can lead to visual sensations. We used fMRI to demonstrate activity in visual cortical areas specifically related to illusory colored and spatially located visual percepts in a synesthetic man who has been completely blind for 10 years. No such differential activations were seen in late-blind or sighted non-synesthetic controls; neither were these areas activated during color-imagery in the late-blind synesthete, implying that this subject's synesthesia is truly a perceptual experience.

Key words: synesthesia, V4/V8, supramarginal gyrus, angular gyrus, blind, color processing

INTRODUCTION

The first known reference to synesthesia is a description of a blind man who described the color scarlet as being "like the sound of a trumpet" (Locke, 1690). In the following centuries, there have been sporadic reports of individual late-blind visual synesthetes, including blind subjects who experienced colored-pitch (Phillipe, 1893), colored-vowel sounds (Galton, 1883), colored-spoken letters, colored words (especially for names), colored music (Starr, 1893), colored-olfaction (Cutsforth, 1925) and colored-Braille (Steven and Blakemore, 2004). These reports provide strong evidence for the notion that synesthesia can persist following blindness and that synesthesia therefore does not require continual associative learning or stimulation in the referred modality in order to be maintained (Steven and Blakemore, 2004).

Due to the behavioral focus of these studies (and the relatively recent emergence of neuroimaging) however, it remains unknown where in the brain is the activity that underlies visual synesthesia in blind subjects, whose visual cortices are no longer stimulated by real visual information. This is of special interest given what *is* known about processing capabilities of the visual cortex following blindness and its tendency to "re-map" to aid in the processing of tactile (Sadato et al., 1996), auditory (Weeks et al., 2000) and even language information (Amedi et al., 2003). Does the visual cortex also continue to generate activity that gives rise to synesthetic color? Specifically, does visual synesthesia (e.g., colored-hearing) in

the blind activate those areas that were previously involved in the processing of real color, including area V4/V8, which is known to be activated during colored-hearing in sighted synesthetic individuals (Nunn et al., 2002)?

To investigate this, as part of a study of visual synesthesia in the blind (Steven and Blakemore, 2004), we used fMRI to determine the neural activations associated with the synesthetic visual experiences of a late-blind synesthete with colored-hearing.

CASE REPORT

JF (right-handed male, 52) suffers from retinitis pigmentosa, which has caused retinal degeneration, with gradually deteriorating vision, which led to complete loss even of basic color sensation 10 years ago. JF has experienced visual synesthesia (in which particular forms of natural stimulation of either the auditory or tactile modality cause idiosyncratic visual color perception) from at least 5 years of age (i.e., since before losing his sight). For instance, JF experiences a form of colored-hearing in which he sees specific colored and spatially located visual percepts when he hears "time-words" (i.e., days of the week or months of the year). Unprompted tests on more than 40 synesthetic stimuli, two months apart, revealed extraordinary consistency of JF's verbal descriptions of his synesthetic colors (97.6%), which strongly suggests that his synesthesia is genuine (Steven and Blakemore, 2004).

TABLE I

List of the time-words spoken to JF, which evoked synesthetic colors, and the abstract non-time words, matched for frequency of usage in the English language (Kucera and Francis, 1967), which did not. All numbers are reported out of a maximum frequency of 69991. The controls heard the same time- and non-time words as did JF, but did not have synesthetic experiences for either category of words.

Time-word	Frequency of time-word usage	Matched word	Frequency of matched word usage
Monday	68	Excellent	68
Tuesday	59	Notice	59
Wednesday	35	Prepare	35
Thursday	34	Protect	34
Friday	60	Stories	60
Saturday	68	Wonder	68
Sunday	102	Becomes	102
January	53	Contrary	53
February	45	Expenditures	45
March	121	Heavy	121
April	73	Master	73
May	1399	Like	1339
June	103	Rates	103
July	66	While	66
August	53	Examples	53
September	60	Learning	60
October	54	Owned	54
November	75	League	75
December	53	Unusual	63

To determine which areas of JF's brain might be involved in the generation of his illusory colored percepts, we conducted an fMRI study. A pseudo-random block design paradigm was used to investigate three conditions. The first condition consisted of JF listening to "time-words" (see Table I), each of which evoked the impression of a colored "rectangular blob", spatially localized at a distinct position in the "visual field" of JF's mind's eye. During the second condition, JF listened to abstract words that were matched for frequency of usage to the time-words (Kucera and Francis, 1967) but which did not evoke synesthetic percepts (e.g., 'notice' and 'prepare'; see Table I). Each block in each condition consisted of listening to 12 time-words or 12 non-time-related words spoken for 24 seconds, with 18 seconds of rest (the third condition) separating the blocks. There were 24 blocks in total for each condition. Within the blocks for condition one and two, the subject performed a one-back matching task to ensure that he maintained attention constantly. Subtraction of the cortical activation measured during performance of condition two (listening to non-time words) from the cortical activation measured during performance of condition one (listening to time-words) was expected to reveal only activity related to the synesthetic impressions.

fMRI images were acquired using a Siemens Sonata 1.5T MRI machine with an interleaved multislice gradient echo EPI sequence. Each volume consisted of 35 contiguous axial slices collected from the whole brain, with an in-plane resolution of  $3 \times 3$  mm and a slice thickness of 3 mm, covering the whole brain (matrix =  $64 \times 64$ , TR = 3 sec, TE = 50 msec). Analysis was performed

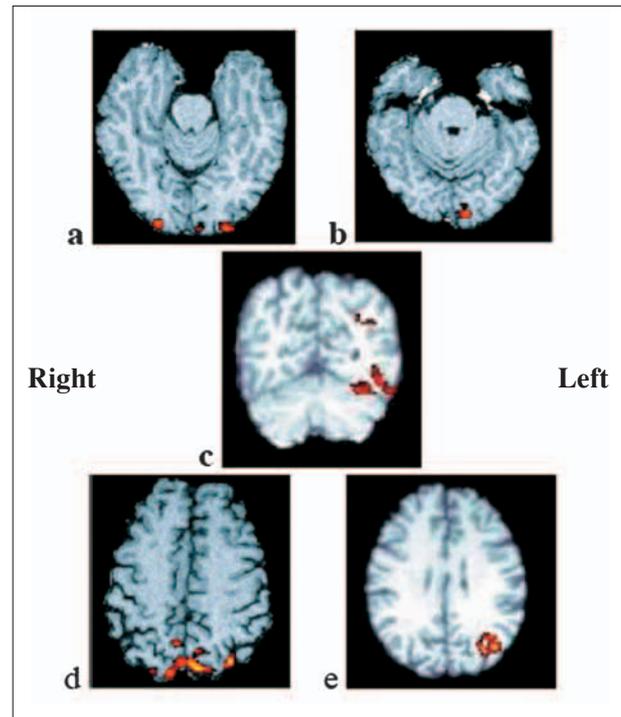


Fig. 1 – Neural activations in response to time-words (vs. non-time words) in the late-blind synesthetic subject, JF. Horizontal sections are shown in radiological convention – left side on the right – with regions of interest in red-yellow. (a) axial plane  $z = 8$ . Bilateral BA 18:  $-26, -98, 8$  and  $24, -98, 8$ ; left BA17 is located between. (b) axial plane  $z = -4$ . Left BA 17 (striate cortex):  $-14, -93, -4$ . (c) coronal plane:  $y = -64$ . Activations: left V4/V8 (BA19)  $-30, -66 -20$ , left BA19  $-42 -66 -14$ , left angular/supramarginal gyri:  $-40, -70 -30$ . (d) axial plane  $z = 64$ . Bilateral superior parietal lobule BA 7:  $-8, -56, 64$  and  $10, -60, 64$ . (e) axial plane:  $z = 28$ . Left angular/supramarginal gyri  $-40, -70, 30$ . All coordinates are reported in standard MNI space (Evans et al., 1992).

using the freely available FMRIB Software Library 5.1 [Functional Magnetic Resonance Imaging of the Brain (FMRIB) Centre; Oxford, UK] with the following standard pre-processing steps: motion correction, spatial smoothing (FWHM = 3 mm), mean-based intensity normalization and nonlinear high-pass temporal filtering (sigma = 45 s). Statistical analysis used FILM, by fitting a 2-event general linear model and applying a local autocorrelation correction. Statistical (Z) maps were thresholded at  $Z > 2.3$ , with a corrected cluster extent threshold of  $p < .01$ .

Listening to time-words, which evoked spatially localized synesthetic colors for JF, specifically activated regions of his visual cortex, including both "early" areas (left Brodmann area – BA17 – or striate cortex – Figures 1a and 1b – and bilateral BA18 – Figure 1a), as well as more anterior extrastriate regions (left area V4 and left area V8; Figure 1c). Bilateral superior parietal lobule was also activated (Figure 1d), as was the inferior parietal lobule, which contains both the angular and supramarginal gyri (the activation spread throughout both gyri) (Figures 1c and 1e).

No difference in activity was observed in a non-synesthetic late-blind control, who was

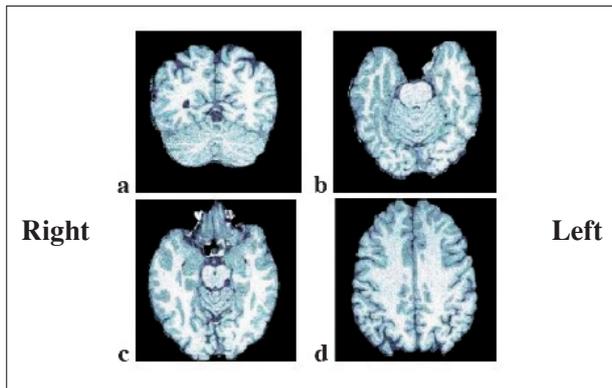


Fig. 2 – Neural activations in visual cortex of late-blind non-synesthetic control in response to time-words (vs. non-time words). Sections are shown in radiological convention – left side on the right – with regions of interest in red-yellow. (a) coronal plane:  $y = -64$ . (b) axial plane  $z = -4$ . (c) axial plane  $z = 8$ . (d) axial plane  $z = 64$ . All planes are reported in standard MNI space (Evans et al., 1992).

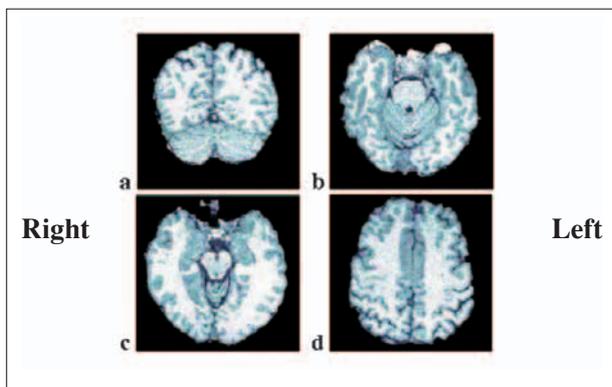


Fig. 3 – Neural activations in visual cortex of a sighted non-synesthetic control in response to time-words (vs. non-time words). Sections are shown in radiological convention – left side on the right with regions of interest in red-yellow. (a) coronal plane:  $y = -64$ . (b) axial plane  $z = -4$ . (c) axial plane  $z = 8$  (d) axial plane  $z = 64$ . All planes are reported in standard MNI space (Evans et al., 1992).

matched for gender, handedness, age, education level, age of onset of blindness, age at commencement of Braille learning and etiology of blindness – retinitis pigmentosa (Figures 2a-d). Neither was a difference in activation seen between listening to time-related words and non-time-related words for a gender, handedness, age and education-level matched sighted non-synesthete (Figures 3a-d).

It should be noted that the lack of differential activation in the control subjects is not merely due to a signal-to-noise difference between the subjects, as revealed by the following statistical comparison. The areas of activation in JF's brain during this experiment were used to create a mask (binarized and normalized to Talairach space and then converted into subject space for each of the controls) and the signal-to-noise ratio within the masked area was determined for each of the subjects during all the active conditions as compared to all the rest conditions. Unlike with JF,

there was no significant difference in BOLD signal between active conditions and rest in PH and CW. For each of the three subjects (including JF) there was also no significant difference in the noise estimates between the active and the rest conditions. The lack of differential activity in the visual cortex for the two controls thus lends strong support to our conclusion that the visual cortex activation apparent in JF is associated with his synesthetic percepts and is not merely due to visual imagery associated with time-words.

Further support for this conclusion comes from a second study we conducted on JF during active visual imagery of color. While studies of other types of imagery (e.g., imagining faces or places) reveal that the same areas that subserve a specific perception (e.g., seeing faces or places) also become activated during imagery (e.g., O'Craven and Kanwisher, 2000), this is not the case with color-imagery. Howard et al. (1998) revealed an area anterior to V4, but not V4 itself, in the right fusiform gyrus (BA 19) that is selectively activated during color-imagery. Furthermore, Bartolomeo et al. (1998) and Shuren et al. (1996) both report patients with achromatopsia following lesions to occipito-temporal cortex who retained the ability to imagine colors, and they theorize that anterior fusiform areas (or areas in the ventral parietal cortex; Bartolomeo et al., 1998) might be involved in color imagery. Because of this dissociation between the neural anatomy for imaging *versus* perceiving color, we sought to determine whether JF's synesthesia might result from color-imagery, rather than being equivalent to real color-perception, by comparing the patterns of activation for synesthetic colors and for imagined colors.

Neural activity recorded during active color imagery was compared to rest in a standard block design. Active conditions consisted of the instructions to imagine a sweater of a particular color, followed by 28 seconds of silence during which time JF actively imagined that color. JF was instructed to continue imagining the colored sweater until he received another instruction, either to imagine a differently colored sweater or to "rest and relax" (this rest/control block lasted for 18 seconds). The task of imagining colored sweaters was chosen because JF remembered that sweaters were the items that he could most clearly see in color before he became blind (he reported that he used to hold a sweater up to his eyes in the morning to choose which one to wear). The comparison of activation recorded during the blocks of color imagery with that during rest blocks revealed activity in an area in the rostral portion of the fusiform gyrus, (BA 19) anterior to V4 (Figure 4). This region of activation is strikingly similar in  $y$  and  $z$  coordinates to that described by Howard et al. (1998) for color imagery in normal sighted subjects. Interestingly, the activation in JF was left lateralized, whereas

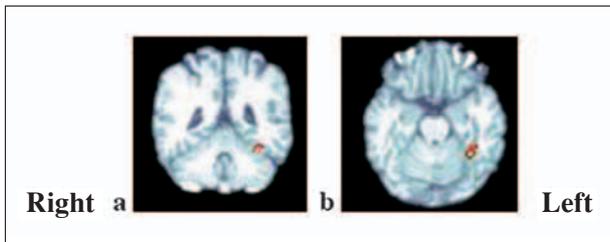


Fig. 4 – Neural activation in visual areas during visual imagery of color (vs. rest) in the late-blind synesthetic subject, JF. Image shown in radiological convention – left side on the right – with region of interest in red-yellow. Activation: Left fusiform gyrus, BA 19 (anterior to V4):  $-38, -48, -20$ . (a) coronal plane  $y = -48$  (b) axial plane  $z = -20$ . All coordinates are reported in standard MNI space (Evans et al., 1992).

Howard et al. described it as predominantly right-sided. Given the fact that ours is a single-subject study, this difference in lateralization might be idiosyncratic, but it could conceivably be due to a lateralization shift occurring as a result of the reorganization of JF's visual cortex following blindness, in line with the general left-dominance of visual activations that we saw during synesthetic experience.

The most important point is that the area activated during color imagery in JF, just as in sighted individuals, was substantially anterior to the classical V4/V8 region, which was activated during JF's synesthetic color perceptions in Experiment 1. This strengthens the interpretation that his synesthetic experiences are not simply the result of visual imagery triggered by the inducing stimulus, but result from activity in the region of visual cortex that is active during the explicit perception of color in normal observers.

## DISCUSSION

The cortical activity reported here during the experience of colored-hearing synesthesia in the late-blind synesthetic subject, JF, is consistent with previous literature concerning activations associated with color perception and with visual synesthesia in the sighted. Areas V4 and V8 are activated by genuine colored stimuli in sighted subjects (McKeefry and Zeki, 1997; Hadjkhani et al., 1998), and Nunn et al. (2002) have described activation of V4/V8, selectively on the left side, during the perception of synesthetic color in sighted synesthetes. Nunn et al. (2002) also observed left-lateralized inferior parietal lobule (including the angular gyrus) in their synesthetes (but not controls) during the perception of colored-hearing synesthesia.

Nunn et al. did not report activity in primary visual cortex, although Aleman et al. did see V1 (but not V4/V8) activation during synesthetic color experience in an fMRI study of one colored-hearing synesthete. Perhaps the activation of early visual

areas in JF is related to the fact that his synesthetic percepts take the form of distinct shapes, localized in space. It is also conceivable that the activation of V1 is related to the processing of language in JF. There is evidence that left lateralized BA 17 is activated during language processing tasks in both late-blind (Burton et al., 2002) and congenitally blind subjects (Amedi et al., 2003). Furthermore, transcranial magnetic stimulation of the occipital pole interferes with Braille reading in the blind (Cohen et al., 1997). It might be significant that much of the synesthesia-specific activation seen in JF is left lateralized (including BA 17, the angular/supramarginal gyri and V4/V8): this might be related to the fact that he (like most synesthetes with colored hearing) sees synesthetic color in response to certain words, as opposed to all sounds. Other functions that involve language and color, like color-naming are also thought to be left-lateralized. Lesions to both the left lingual and hippocampal regions can be associated with a deficit in color naming (Damasio and Damasio, 1983) without achromatopsia.

It must be remembered that the control stimuli in our experiment were also words. So, even if language processing is involved in the activations seen in BA 17 and elsewhere in the left hemisphere, it must also be specifically related to the synesthetic visual experience, perhaps through some kind of association or "binding" of the linguistic meaning and the colored percept. This might be particularly the case for the activity seen in the angular gyrus, which is thought to be involved in integrating visual and semantic language information in the sighted (Horwitz et al., 1998; Clark et al., 2000). Damage to the left angular gyrus often causes agraphia and/or dyscalculia as well as deficits in spatial imagery and left-right orientation (Gerstmann, 1927; Carota et al., 2003; Mayer et al., 1999). It is, then, not surprising that it is activated in JF during the perception of his spatially located colored-percepts induced by language stimuli. Indeed, Ramachandran and Hubbard (2001) originally proposed the angular gyrus as a candidate area for synesthetic processing in what they call "higher" synesthetes whose synesthesia is triggered by a higher cognitive characteristic of the inducing stimulus, such as its semantic quality.

The fact that JF's synesthetic experiences take the form of shapes, localized in the left or right periphery of his "visual field", could be reflected in the bilateral activation of BA 18 as well as the superior parietal areas (bilateral BA 7), which are known to be involved in visual spatial localization (Haxby et al., 1991). The left superior parietal gyrus can also be activated during color discrimination (Gulyas and Roland, 1991), making it a good candidate for the integration of color and spatial information.

We therefore suggest that the array of activations seen in JF, including their lateralization,

correlate well with his synesthetic experiences of localized colored shapes, and the association between these percepts and the linguistic analysis underlying the synesthesia.

Studying visual synesthesia in a late-blind subject using fMRI offers us a unique window into the residual functioning of the visual cortex of the blind and reveals not only that regions of the visual cortex retain their selective capacity to process visual information about form, color and spatial location in the late-blind, but also that activity in these areas can be associated with explicit, conscious visual perception, even after 10 years without genuine visual experience. Furthermore, these data provide evidence for the claim that synesthetic experiences are truly perceptual, rather than simply the result of imagination.

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