PHYSIOLOGY/IMAGING

NEURONAL CORRELATES OF COLOUR-GRAPHEMIC SYNAESTHESIA: A fMRI STUDY

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Abstract

Synaesthesia is a perceptual phenomenon in which specific events in one sensory modality induce experiences in another. In colour-graphemic synaesthesia, subjects report colour experiences induced by written letters. Our subjects displayed this type of synaesthesia, as verified by a test of the consistency of the perceptual associations over time, and had no history of neurological or psychiatric disorders. We investigated the hypothesis that the synaesthetic colour experience is accompanied by an activation of the human colour area (V4/V8) using functional magnetic resonance imaging (fMRI). With retinotopic and colour mapping we could confirm that colour stimuli specifically activate area V4/V8. For the study of colour-graphemic synaesthesia we used an AB boxcar design with blocks of letters that elicited a synaesthetic colour experience (condition A) alternating with blocks of letters that did not (condition B). In both hemispheres condition A led to a significantly higher activation of V4/V8 than condition B. These findings support the hypothesis that the grapheme-induced colour perception in synaesthesia is caused by an activation of the colour areas of the human visual cortex.

Key words: retinotopic mapping, colour mapping, colour-graphemic synaesthesia experiment

Introduction

Synaesthesia is a heterogeneous phenomenon (Baron-Cohen et al., 1987; Cytowic, 1989; Grossenbacher and Lovelace, 2001; Emrich et al., 2002; Rich and Mattingley, 2002) in which, specific events in one sensory modality involuntarily and automatically induce experiences in another. There is robust experimental evidence for the specificity and stability of synaesthetic experiences (Baron-Cohen and Harrison, 1997; Cytowic, 1989). However, recent psychophysical findings suggest that mechanisms of attention also influence synaesthetic experiences (Rich and Mattingley, 2003) and that synaesthesia depends on the conceptual level of representation (Ward and Simner, 2003).

In this study, we focus on colour-graphemic synaesthesia, a condition in which synaesthetes report vivid colour experiences induced by written letters. Our working hypothesis is that these colour experiences are associated with the activation of these parts of the visual cortex that are held responsible for the processing of colour information (Nunn et al., 2002). In the literature these areas have been identified as V4 (Zeki and Marini, 1998; Bartels and Zeki, 2000) or V8 (Hadjikhani et al., 1998). Based on the evidence that these areas (V4/V8) are relevant for colour perception (Schoenfeld et al., 2002; Morland et al., 1999), we focused on a region of interest (ROI) analysis of this specific area.

Recent functional imaging studies have investigated the activation of the human colour centre in the context of coloured-hearing, another form of synaesthesia. In this case spoken words induce colour experiences (Baron-Cohen et al., 1987). Using Positron Emission Tomography (PET) Paulesu et al. (1995) observed activation of visual association cortex in coloured-hearing synaesthetes. However, in this study no significant activation of lower visual areas, including areas V1, V2 or V4/V8 has been detected. Taking advantage of the greater spatial resolution and sensitivity of fMRI, Nunn et al. (2002) repeated the experiments by comparing brain activation patterns elicited by spoken words *versus* tones in synaesthetes and controls. Their findings revealed activation of V4/V8 in the left hemispheres of synaesthetes but not controls.

Using fMRI, Elias et al. (2003) demonstrated differences in brain activation during psychophysical tasks performed by a colour-graphemic synaesthete and a control. The synaesthete showed significant activation along the left dorsal visual stream (including Brodmann's Area 19, 7, 39 and 40), while there was no such activation in the control. Whether colour-graphemic synaesthesia elicited by written letters is also associated with an activation of V4/V8 is unknown. The purpose of the present study was to resolve this question.

Aims and Design

Using fMRI we investigated whether colour experiences of synaesthetes elicited by written

letters are accompanied by an activation of the human colour centre V4/V8.

Retinotopic Mapping

In order to determine the borders of V4/V8 for each of our subjects (Sereno, 1994; Hadjikhani et al., 1998) we applied the technique of polar-angle mapping of early visual areas as reported by Goebel et al. (1998).

Colour Mapping

Additionally we have used colour mapping in order to confirm that colour stimuli specifically activate the areas identified as V4/V8 in each of our subjects. Blocks of coloured and achromatic Mondrians were presented in alternation in an AB boxcar design (a modified version of the colour mapping experiment of Nunn et al., 2002), five of each type over 260 scans (520 sec). Luminance of coloured and achromatic Mondrians was adapted using a LiteMate/SpoteMate photometer system (Photo Research Inc., CA, USA). Ten Mondrians were presented in each block, each for 3 sec. These were followed by a grey isoluminant screen for 1 sec to avoid motion cues at transitions to the new patterns. Between each block a fixation cross was presented for 10 sec.

Colour-Graphemic Synaesthesia

In order to determine whether the colour centre identified by retinotopic and colour mapping is activated during the experience of colour-graphemic synaesthesia, we used an AB boxcar design with blocks of letters that elicited a synaesthetic colour experience (condition A) and blocks of letters that did not (condition B). Each subject gave us a list of three letters inducing colour-graphemic synaesthesia. Attempting to control for shape complexity, we additionally selected three letters that did not induce colour-graphemic synaesthesia but were similar in shape. These letters possessed achromatic synaesthetic qualities (the experience of transparent grey or anthracite). Blocks of the same type (A or B) were shown five times over 204 scans (408 sec). Ten letters were presented in each block in pseudorandom order, each for 2.5 sec, followed by a grey isoluminant screen for .5 sec. Between each block a fixation cross was presented for 10 sec.

Subjects

We studied a cohort of 4 subjects who had been identified as colour-graphemic synaesthetes according to the test of the consistency of the perceptual associations over time (a modified version of the test of genuineness for synaesthesia; Baron-Cohen et al., 1987). These tests were performed on the basis of a list of letters that did or did not induce colour experiences. Subjects had no history of neurological or psychiatric disorders.

Visually presented graphemes evoked synaesthesia in all our subjects. When seeing words, they reported to perceive a sequence of colours according to the sequence of letters they were shown. Grapheme shape did not largely determine their colour experience, e.g. “O” and “0” or “C” and “U” had different colours. Listening to spoken letters as well as spelling words induced synaesthetic colour experiences in our subjects as well.

They all reported to see the synaesthetic colour only in their mind’s eye and not to project it externally. They were able to access both “real” and synaesthetic colours equally easily and closing their eyes did not induce more vivid colour experiences.

Two of our subjects (subjects 1 and 2) reported to perceive a flat screen of colour in their mind’s eye while seeing letters inducing synaesthesia. The two others (subjects 3 and 4) reported that the shape of their colour experience rather resembles a blurry version of the letter’s shape they looked at.

Method

All fMRI measurements were performed with a 1.5 T MAGNETOM Vision MRI scanner (Siemens Medical Systems, Erlangen, Germany) equipped with a standard head coil.

For functional imaging, we used a gradient echo planar imaging (EPI) sequence [(TR/TE) = 2000 msec / 60 msec, (FA) = 90°, (FoV) = 200 × 200 mm^2, voxel size 3.13 × 3.13 × 3 mm^3]. Each scan comprised the acquisition of 260 volumes (colour-mapping experiment) and 204 volumes (colour-graphemic synaesthesia experiment), respectively (one volume = 16 axial slices covering the occipital and inferior temporal cortex). A T1-weighted anatomical FLASH (fast low-angle shot) scan was recorded in the same session for each subject (matrix = 256 × 256; slice thickness 1 mm, 180 slices; voxel dimensions 1 × 1 × 1 mm). Data analysis, registration and visualisation were performed with the fMRI-software package BrainVoyager QX (Brain Innovation, Maastricht, the Netherlands) (Goebel et al., 1998).

Anatomical Data

Talairach Transformation

For each subject the 3D-FLASH recordings were transformed into Talairach space. This Talairach transformation was performed in two steps. At first the 3D data set of each subject was aligned with the stereotaxic axes by specifying the location of the anterior (AC) and posterior commissure (PC) manually. In the second step the

extreme points of the cerebrum were specified and used together with AC and PC coordinates to scale the 3D data sets into the dimensions of the standard brain of the Talairach and Tournaux atlas (1988).

Surface Reconstruction

The 3D-FLASH recordings were used for surface reconstruction of both hemispheres (Muckli et al., 2002; Kriegeskorte and Goebel, 2001; Linden et al., 1999). The white/grey matter border was segmented with a region-growing method. It was tessellated using two triangles for each side of a voxel located at the margin of white matter. The reconstructed surface was then subject to iterative corrective smoothing. This iterative morphing algorithm (Goebel et al., 1998) let the surface grow smoothly into the grey matter. The resulting surface was used as a reference mesh for the visualization of functional data. The iterative morphing algorithm was further used to inflate each hemisphere. Each inflated hemisphere possesses a link to the folded reference mesh so that functional data can be shown at the correct position of the inflated representation. Displaying functional maps on an inflated hemisphere permits the topographic representation of the three-dimensional pattern of cortical activation without loosing the lobular structure and the gyral patterns of the telencephalon.

Functional Data

Prior to statistical analysis, the functional data were preprocessed as follows: the temporal slice scan time shift was corrected by using the first scan time within a volume for alignment by linear interpolation in the following slices of that volume. A Talairach transformation (Prvulovic et al., 2002) was performed for the complete set of functional data of the subject (three functional runs), yielding a 4-D data representation (volume time course: 3 × space, 1 × time). The time-series of functional images was aligned in order to minimize the effects of head movements. The central volume of the time-series was used as a reference volume to which all other volumes were aligned, using a 3-D motion correction that estimates the three translation and three rotation parameters of rigid body transformation. Temporal smoothing was applied to EPI images with linear trend removal and temporal frequency-based (fast Fourier transform) high-pass filter of 3 cycles per time course.

The statistical analysis was based on the application of multiple regression analysis to time series of task-related functional activation (Friston et al., 1995). The general linear model (GLM) of the experiment was computed for each of the 3 volume time courses (colour mapping, colour-graphemic synaesthesia and retinotopic mapping).

Polar Angle Mapping

Retinotopy of polar angle was revealed with cross correlation analysis selecting the lag value resulting in the highest correlation value for a particular voxel. The obtained lag value finally determined the pseudocolour for that voxel as well as for corresponding polygons on reconstructed surfaces (Goebel et al., 1998; Muckli et al., 2002).

Colour Mapping and Colour-Graphemic Synaesthesia

In the colour mapping experiment, the signal values during the coloured and the isoluminant achromatic Mondrian stimuli were considered the effects of interest. In the colour-graphemic synaesthesia experiment the effect of interest were the signal values during the presentation of letters that did and did not induce synaesthetic experiences, respectively. The corresponding predictors, obtained by convolution of an ideal box-car response (assuming a value 1 for the volume of task presentation and a volume of 0 for the remaining time points) with a linear model of the hemodynamic response (Boynton et al., 1996), were used to build the design matrix of the experiment. To analyze the effect of conditions compared to baseline, 3-D statistical maps were generated by associating each voxel with the F value corresponding to the specific set of predictors and calculated on the basis of the least mean squares solution of the GLM. The obtained p values were then corrected using the false discovery rate (FDR) (Genovese et al., 2002). The statistical maps are based on a fixed effects analysis. Statistical results were visualized as 3-D statistical maps on a surface reconstruction of the subject's brain. Effects were only shown if p (corrected for FDR) was $< .05$ for one of the conditions compared to baseline.

As ROI we defined the significantly activated clusters in left and right V4/V8 (as revealed by retinotopic mapping) which showed overlapping colour-specific activity in the colour mapping as well as in the colour-graphemic synaesthesia experiment.

We analyzed the signal of every ROI by first averaging the data (time courses) of all voxels constituting the ROI and then computing statistical parameters for the time course on the basis of the GLM. The ROI-GLMs were corrected for serial correlations within the ROI time course. The ROI-GLM results included the F value for the explained variance of the model (after the variance explained by the different signal levels had been removed) and the t value for the comparisons of the beta weights of each current predictor (effect of conditions compared to baseline). We also performed contrast analysis, based on the t test of differences (*a priori* alpha error of $p < .05$)

between the beta weights of both predictors to identify clusters that showed a higher activity for letters inducing synaesthesia when compared to letters not inducing such experiences (colour-graphemic synaesthesia experiment). The same contrast analysis was repeated to identify clusters that showed higher activity in the colour Mondrian condition than the achromatic Mondrian condition (colour mapping experiment).

In order to rule out whether a global BOLD change during the colour-graphemic synaesthesia condition led to a local change in V4/V8 we did a region of interest analysis on other visual areas as well (V1, VP). The published coordinates (V1, VP) of Hasnain et al. (1998) were used as a reference.

Results

In all subjects the polar-angle retinotopic map permitted us to delineate V4/V8 in both hemispheres (see Figure 1 as example) and to confirm that the ROIs used for contrast analysis overlapped with area V4/V8 as identified with retinotopic mapping.

As exemplified in Figure 2 the significant BOLD signal changes for coloured Mondrians *versus* baseline (A) also overlapped with the significant BOLD changes, for letters inducing synaesthetic colour experiences *versus* baseline (B) ($p < .05$, corrected for FDR in all conditions). Thus, regions identified as V4/V8 were selectively activated by coloured stimuli and the presentation of letters giving rise to the experience of colour.

The comparison of ß-values between the condition that gave rise to the experience of colour and the control condition in other selected regions of the visual system (V1, VP) did not show consistent increase during the colour-graphemic synaesthesia condition comparable to the identified increase in V4/V8. Even a decrease during colour-graphemic synaesthesia can be reported in VP.

Tables I and II summarize the Talairach coordinates of the activated ROIs with the statistical values of the ROI-GLM and the results of the contrast analyses between the corresponding conditions.

In the colour mapping experiment the ROI-GLM based contrast analysis between coloured and achromatic Mondrians revealed a significantly higher BOLD-signal activation for the coloured Mondrian condition in both, left and right V4/V8. In the colour-graphemic synaesthesia experiment there was a higher BOLD-signal change in V4/V8 for the synaesthesia-inducing letters than for the letters not inducing the experience of colour. This direct comparison was significant ($p < .05$, after correction for serial correlations) in two subjects.

Additionally we found in both subjects (1 and 2) the frontal cortex, the insula, the superior and inferior temporal cortex to be activated in a contrast analysis between the letters evoking

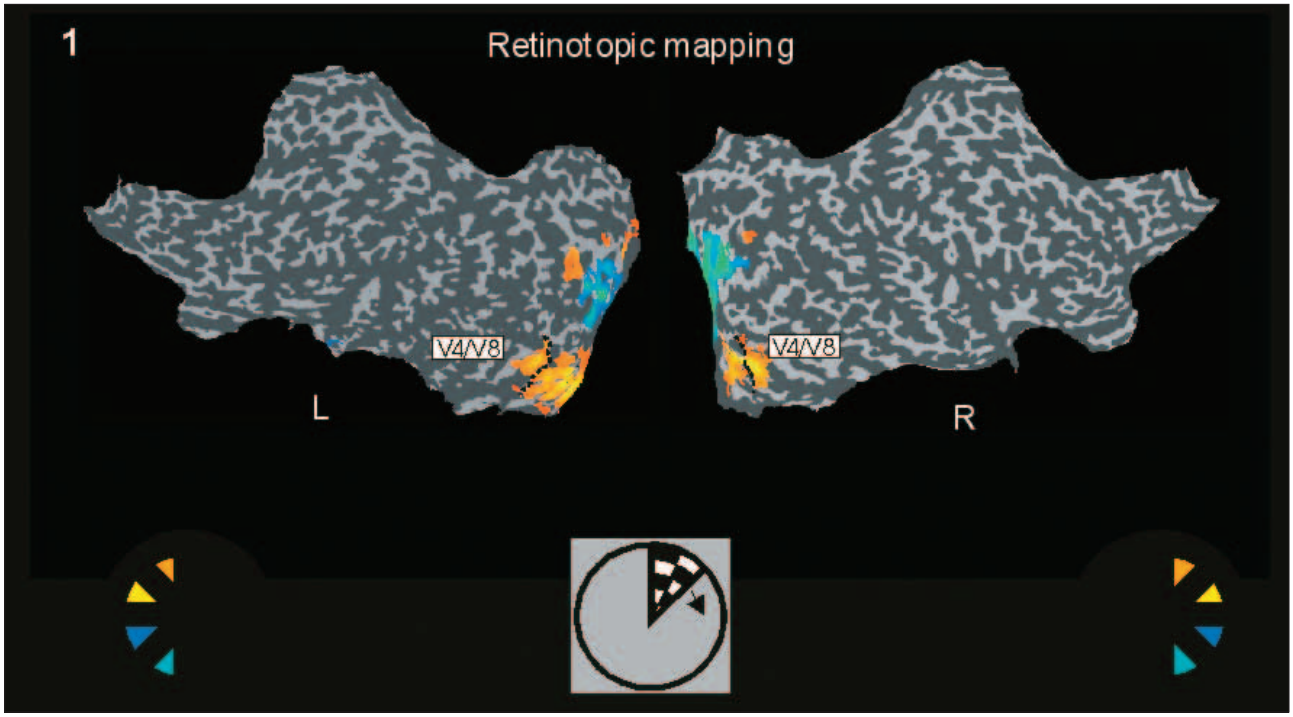

Fig. 1 – *Polar-angle retinotopic mapping. The statistical maps (significance level: $p < .05$ corrected for FDR) are projected onto flatmaps of the left (L) and right (R) hemisphere of the brain of Subject 1. The borders of V4/V8 are marked with dashed lines. Responses to stimulation in the right upper visual field are coded yellow (horizontal meridian, hm) to orange (vertical maridian, vm), in the right lower visual field blue (hm) to turquoise (vm), in the left lower field blue (hm) to turquoise (vm) and in the left upper field yellow (hm) to orange (vm).*

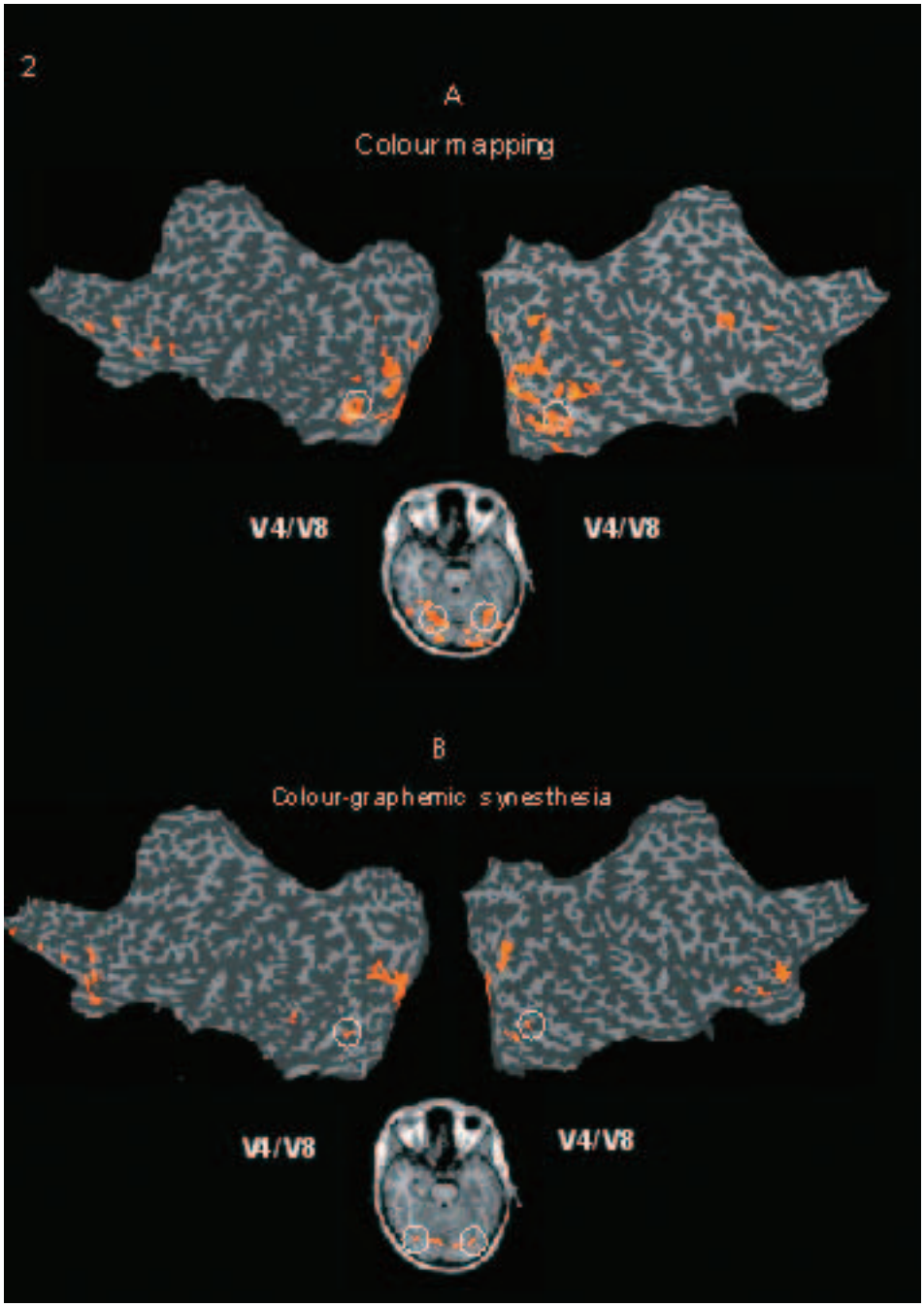

Fig. 2 – *GLM analysis of the fMRI time series in the visual colour mapping experiment (A) and the colour-graphemic experiment (B). Colour-coded statistical maps of BOLD signal increase for the colour-mondrian condition compared to baseline (A) and for the colour-graphemic synesthesia condition compared to baseline (B), superimposed on the same anatomic axial slice ($z = -20$) and on a flat map reconstruction of the subject's brain (Subject 1). All superposition maps at $p < .05$ (corrected for FDR).*

colour-graphemic synaesthesia and letters that did not (see Appendix for details).

Subject 3 only showed significant activation of the inferior frontal and inferior temporal lobe. There were no clusters with significant contrast in the data of subject 4. V4/V8 activation for subject 3 and 4 failed to reach the chosen level of significance in the contrast analysis after correction of serial correlations (data not shown). Direct group analysis was hampered because of insufficient spatial overlap of the ROIs.

Discussion

Cortical Activation during Colour-Graphemic Synaesthesia

Activation of V4/V8 during Colour-Graphemic Synaesthesia

According to reports of synaesthetes their colour experiences resemble real colour percepts rather than colour imagery (Emrich et al., 2002). This

TABLE I
Statistical analysis of V4/V8 activation in colour-mapping and coulour-graphemic synesthesia.

SUBJECT 1

Experiment	Area	Coordinates			Model	Predictor 1		Predictor 2		Contrast	
		x	y	z	F	t	beta	t	beta	t	p
Colour mapping	lV8	– 33	– 68	– 17	6.69	3.51	4.29	.29	.37	3.49	.000557
	rV8	27	– 65	– 17	19.81	4.33	1.09	– 2.31	– 2.528	4.31	.000023
Colour-graphemic	lV8	– 31	– 74	– 20	8.67	3.82	6.19	3.56	5.79	3.82	.000181
synesthesia	rV8	30	– 68	– 20	7.63	3.90	5.75	2.01	2.96	3.90	.000130

SUBJECT 2

Experiment	Area	Coordinates			Model	Predictor 1		Predictor 2		Contrast	
		x	y	z	F	t	beta	t	beta	t	p
Colour mapping	lV8	– 24	– 77	– 12	6.82	3.38	5.62	– .27	– .45	3.37	.000885
	rV8	29	– 78	– 15	9.93	4.46	7.81	1.80	3.17	4.44	.000013
Colour-graphemic	lV8	–– 27	– 70	– 14	7.33	3.83	6.03	2.12	3.35	3.83	.000175
synesthesia	rV8	26	– 79	– 13	8.74	4.02	4.59	3.14	3.58	4.021	.000082

Talairach coordinates for centres of mass of ROIs and ROI-GLM results of the different conditions *versus* baseline: Predictor 1 (colour mapping) = coloured Mondrians *versus* baseline; Predictor 2 (colour mapping) = achromatic Mondrians *versus* baseline. Predictor 1 (colour-graphemic synesthesia) = colour-graphemic synesthesia-inducing letters *versus* baseline; Predicor 2 (colour-graphemic synesthesia) = non colour-graphemic sysnesthesia-inducing letters *versus* baseline. ROI-GLM results included statistical values for the explained variance of the model (F values; $p < .05$, corrected for serial correlation), the beta weights for each predictor (t values; $p < .001$ corrected for serial correlation) and contrast analysis between the two predictors in each experiment (t values; significant at $p < .05$). Each selected cluster comprised an area of max $5 \times 5 \times 5$ mm in Talairach space.

raises the question how true colour vision, colour imagery and synaesthetic experiences differ in their neuronal manifestation (Rich and Mattingley, 2002).

If synaesthetic colour-graphemic experience is in fact similar to true colour percepts, one should expect activation of the human colour centre during the experience of colour by synaesthetes.

In the PET experiment of Paulesu et al. (1995) synaesthetic colour experiences have been found to be associated with activation of regions of the visual cortex addressed as visual association cortex. However, the low resolution and sensitivity of PET (Aine, 1995) precluded identification of the exact areas of the visual cortex. Data had to be subject to group-analysis, and because the position of the colour centre in the human brain differs between subjects (Bartels and Zeki, 2000), precise location of the expectedly small activation foci was not possible. In contrast to these PET data the fMRI-findings of Nunn et al. (2002) suggest that synaesthetic colour experiences are associated with activation of earlier levels of visual cortex. In the condition of coloured hearing these authors found activation of the human colour centre in the left hemisphere. Elias et al. (2003) demonstrated that activation patterns in a colour-graphemic synaesthete and a control differed during psychophysical experiments including a dice arithmetic task and an eyes-closed addition task. However, the design of their study did not enable them to detect activation in early visual areas.

In the present study we first applied retinotopic and colour mapping in order to confirm that colour stimuli specifically activate area V4/V8. We then compared activation patterns induced by letters that did or did not evoke synaesthetic experiences and found that the former led to a significantly higher activation of V4/V8 than the latter. These findings support the hypothesis that the grapheme-induced colour experiences in synaesthesia arise from a coactivation of the colour areas V4/V8 of extrastriate visual cortex. Interestingly, V4/V8 is not differentially activated in colour imagery tasks (Howard et al., 1998). Thus, the neural substrate of synaesthetic colour-phonemic as well as colour-graphemic experience seems to be different from that supporting colour imagery. The fact that synaesthetic experiences go along with activation of an area that is at a low level of the processing hierarchy suggests that synaesthetic experiences are closer to hallucinations (ffytche et al., 1998) than to colour imagery. As shown in a recent fMRI study in schizophrenic patients (Dierks et al., 1999) auditory hallucinations are associated with activation of early sensory areas, in this case the primary auditory cortex.

Lateralization

Analysing colour-phonemic synaesthesia, activation of visual cortex was restricted to the left hemisphere (Nunn et al., 2002). The authors hypothesized that normal colour perception competes with synaesthetic perception in left V4/V8. In our study activation was equally significant in V4/V8 of both hemispheres in Subject 1 and 2. Further experiments with lateralized presentation of the visual stimuli might resolve this issue.

Differences between Subjects

Two of our subjects (subjects 1 and 2) showed significant activation of V4/V8 after correction for serial correlations. Interestingly these subjects reported to perceive a screen in their mind's eye which gets completely coloured whenever seeing a letter inducing synaesthesia. The two other subjects

TABLE II

Subject 1	Coordinates			Predictor 1 (syn)		Predictor 2 (control)	
	x	y	z	β	t	β	t
V4 l	– 31	– 74	– 20	6.19	3.82	5.79	3.56
V4 r	30	– 68	– 20	5.75	3.9	2.96	2.01
V1	0	– 80	– 9	6.168	5.274	6.067	5.187
VP	12	– 70	– 15	6.941	5.507	8.041	6.38
Subject 2	Coordinates			Predictor 1 (syn)		Predictor 2 (control)	
	x	y	z	β	t	β	t
V4 l	– 27	– 70	– 14	6.03	3.83	3.35	2.12
V4 r	26	– 79	– 13	4.59	4.02	3.58	3.14
V1	– 2	– 86	– 5	5.891	5.536	6.038	4.648
VP	19	– 65	– 5	5.472	3.627	4.558	3.021

Talairach coordinates for centres of mass of ROIs (V4r, V4l, V1, VP) and ROI-GLM results of the different conditions *versus* baseline: Predictor 1 (colour-graphemic synesthesia) = colour-graphemic synesthesia-inducing letters *versus* baseline; Predicor 2 (colour graphemic synesthesia) = non graphemic-colour sysnesthesia-inducing letters *versus* baseline. ROI-GLM results included statistical values for the explained variance of the model (F values; $p < .05$, corrected for serial correlation), the beta weights for each predictor (t values; $p < .001$ corrected for serial correlation) and contrast analysis between the two predictors in each experiment (t values; significant at $p < .05$). Each selected cluster comprised an area of max $5 \times 5 \times 5$ mm in Talairach space.

(subjects 3 and 4) reported to perceive their synaesthetic experience in their mind's eye as well. However, they described it rather as a transparent screen with a small and blurry but coloured version of the letter they were shown. One could hypothesize that the phenomenological difference between a small but coloured version of a letter on a transparent screen (condition A) and a small grey/transparent letter (condition B) may not lead to a significant contrast within V4/V8, while the contrast between the completely coloured screen (condition A) and its grey/transparent counterpart (condition B) does.

Additionally Activated Areas

On a contrast map of activation patterns induced by letters that evoked colour-graphemic synaesthetic experiences (condition A) and letters that did not (condition B) we additionally found the inferior frontal gyrus, the insula, the superior and inferior temporal gyrus to be activated. Activation in superior temporal lobe and the insula has already been detected during colour-phonemic synaesthesia experiments (Paulesu et al., 1995). Grossenbacher and Lovelace (2001) hypothesized that multisensory regions within the superior temporal lobe (Benevento et al., 1977; Bruce et al., 1981; Hikosaka et al., 1988), might be strong candidates for mediating pathway convergence during the induction of a synaesthetic-colour experience, which leads to a feedback-activation of visual areas responsible for the perception of colour (disinhibited-feedback theory). In our study we additionally found the inferior temporal lobe to be activated during colour-graphemic synaesthesia. Antecedent anatomical and physiological studies have established that this region is part of a cortical colour processing system (Komatsu et al., 1992; Heywood et al., 1995), which seems to extend from the striate cortex through area V2 to V4/V8, and beyond to the inferior temporal and frontal cortex (Zeki and Marini, 1998). This third stage of colour processing, based on the inferior temporal and frontal cortex seems to be especially concerned with object colours (Zeki and Marini, 1998). Chao and Martin (1999) were able to show that retrieving information about object colours activates the inferior temporal and frontal cortex. Frontal activity in colour-graphemic synaesthetes has also been described by Schiltz et al. (1999) who used scalp-recorded event-related potentials to examine neural responses associated with the detection of visually presented letter stimuli. Their results indicate that the experience of synaesthetic colours is associated with activity evoked considerably later than that triggered by the inducing letter, and might arise initially from frontal brain areas.

The fMRI-block-design of our study however, does neither enable us to make assumptions on the chronological order of cortical activation during colour-graphemic synaesthesia, nor can it support or rule out theories that posit normal connectivity (Grossenbacher and Lovelace, 2001) or additional cortical interconnections (Maurer, 1997) for the experience of synaesthesia.

Concluding remarks

This study is the first demonstration of the coactivation of the human colour centre in colour-graphemic synaesthesia. It confirms and extends previous evidence obtained with colour-phonemic synaesthesia (Nunn et al., 2002). A challenge for future studies of synaesthesia will be the identification of the pathways that mediate this activation of early visual areas and to determine whether this coactivation occurs before or after semantic decoding of the colour inducing stimuli. Applying advanced imaging techniques such as event-related fMRI with high temporal resolution might be one of the options to resolve these questions.

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Addendum

After our manuscript was accepted for publication we learned of the paper by Hubbard et al. (*Neuron, 45:* 975-985, 2005) reporting similar findings.

For your information, the full reference is: Hubbard EM, Arman AC, Ramachandran VS and Boynton GM. Individual differences among grapheme-color synesthetes: Brain-behavior correlations. *Neuron, 45:* 975-985, 2005.

Appendix

TABLE III

Additionally activated areas (Contrast map); Subject 1

Area	Cluster size	Coordinates			Model	Contrast	
		x	*y*	*z*	*F*	*t*	*p*
IFG	745	– 32	48	19	20.187	6.358	.00
	679	30	49	19	5.173	2.971	.003329
Insula	703	– 41	8	10	9.179	4.214	.000038
	711	44	7	0	3.904	2.782	.005930
STG	790	– 48	10	4	2.618	2.286	.023293
	541	52	14	– 2	5.435	3.111	.002137
ITG	125	– 56	– 15	– 16	2.276	3.845	.000162

TABLE IV

Additionally activated areas (Contrast map); Subject 2

Experiment	Cluster size	Coordinates			Model	Contrast	
		x	*y*	*z*	*F*	*t*	*p*
IFG	104	– 44	19	7	5.694	3.086	0.002317
	378	42	40	18	1.916	1.680	0.094450
Insula	292	39	3	4	4.806	2.511	0.012834
STG	146	– 50	16	0	4.650	2.293	0.022918
	561	52	15	2	4.961	2.772	0.006099
ITG	179	63	– 22	– 10	5.044	3.155	0.001857

TABLE V

Additionally activated areas (Contrast map); Subject 3

Area	Cluster size	Coordinates			Model	Contrast	
		x	*y*	*z*	*F*	*t*	*p*
IFG	1057	30	42	19	2.120	2.074	0.039360
Insula							
STG							
ITG	1089	63	– 11	– 21	3.242	2.546	0.011646

Talairach coordinates for centres of mass of clusters with significant contrast between different conditions: Predictor 1 (colour-graphemic synesthesia) = colour-graphemic synesthesia-inducing letters *versus* baseline; Predicor 2 (colour- graphemic synesthesia) = non colour graphemic synesthesia-inducing letters *versus* baseline. ROI-GLM results included statistical values for the explained variance of the model (F values; $p < .05$, corrected for serial correlation), the beta weights for each predictor (t values; $p < .001$ corrected for serial correlation) and contrast analysis between the two predictors in each experiment (t values; significant at $p < .05$). Each selected cluster comprised an area of max $5 \times 5 \times 5$ mm in Talairach space. IFG (inferior frontal gyrus), STG (superior temporal gyrus), ITG (inferior temporal gyrus).