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Activation of striate cortex in the absence of visual stimulation: an fMRI study of synesthesia

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It has been suggested that internally generated visual perception involves the primary visual cortex V1. To test this hypothesis, a functional MRI study was conducted with a female subject with orthographic color–word synesthesia. This subject was selected as she reported clear involuntary visualization of auditorily presented verbal material. Hearing a word resulted in seeing the word in a particular color. fMRI scans were acquired while the subject performed two verbal tasks (passive listening to words and verbal fluency). Significant activity was detected in primary visual cortex, in the absence of external visual stimulation. This finding provides evidence for a role of modulatory feedback connections between associative and primary visual areas in visual experience without direct visual stimulation. *NeuroReport* 12:2827–2830 © 2001 Lippincott Williams & Wilkins.

Key words: Brain mapping; Hallucinations; Mental imagery; Primary visual cortex; Synesthesia

INTRODUCTION

Synesthesia occurs when stimulation in one sensory modality automatically triggers a perceptual experience in a second modality [1]. The most common form of synesthesia appears to be hearing words and seeing them in color, which has been called colored hearing [2]. The study of the neural basis of synesthesia is of interest to neuroscientists, as it may elucidate the physiology involved in visual perceptual experiences without direct external input to the visual system. In addition, neuroimaging studies of synesthesia may shed more light on the neural basis of integrated cross-modal perception. The consistency with which visual processing can be elicited in word–color synesthesia provides an interesting case for examining visual cortex activation in the absence of external visual stimulation. Brain activation was measured with fMRI during two different verbal tasks, in a subject with color–word synesthesia. More specifically, the hypothesis was tested whether primary visual cortex would be activated during the processing of auditorily presented verbal material.

MATERIALS AND METHODS

Subjects: A 32-year-old right-handed woman who reported orthographic color–word synesthesia from early childhood gave her informed consent to participate in the fMRI study. She had no history of neurological or psychiatric illness and was not taking any psychoactive medication. Evidence for genuine color–word synesthesia was obtained with the alphabet–color test (part of the battery of tests described by Baron-Cohen *et al*. [2]) in which the subject is asked which color she experiences for each letter of the alphabet. According to the criterion of stable cross-modality association [2], the colors reported for each letter should be demonstrated to be highly stable across a considerable period of time. The subject was tested on two occasions: the first time, when she was initially seen at our Department, and 2 years later when she participated in the fMRI experiment. For every letter of the alphabet she reported a different color, and the stability of these cross-modality associations was 96% (i.e. for one letter she reported a different color on the second occasion). A neuropsychological examination revealed a profile that has been described to be characteristic of synesthetes [1]: left–right confusion, mathematical problems and an exceptionally good memory for geometrical figures. Apart from these differences, her neuropsychological test profile was within the normal range.

Instrumentation and Procedure: Brain activation was measured using a 3D BOLD technique (navigated PRESTO sequence [3]: TE/TR 36/24.5 ms, flip angle 10°, matrix $52 \times 64 \times 26$, voxel size 3.51 mm isotropic, scan time 2.4 s) implemented on a Philips ACS-NT 1.5 T scanner with

PT6000 gradients (Philips Medical Systems, Best, The Netherlands). For display of functional activity an anatomical image was acquired at the end of the session (3D-FFE, voxel size $1 \times 1 \times 1.2$ mm). Two tasks were used that targeted the experience of color–word synesthesia in an active condition, but not in a control condition: (1) passive listening to auditory presented words, and (2) verbal fluency. During pretesting of the tasks outside the scanner room, the subject reported strong synesthetic experiences for the active conditions of the tasks, but not for the control conditions. The responses given by the subject were covert to prevent movement artifacts. The subject was blindfolded during performance of the tasks in the scanner. All stimuli were presented by earphones. Both tasks consisted of 14 active and 14 control epochs arranged in an alternating sequence (duration of each epoch condition 21.6 s). During the active condition of task one, 14 words were presented. In the control condition, single pure tones were presented at frequencies of 900 and 950 Hz and the subjects had to react with a button-press to each change of frequency. This task was chosen to achieve a state of vigilance similar to that during the active tasks. During the active condition of task two (verbal fluency) a single letter was presented auditorily and the subject had to generate as many words as possible beginning with that letter, for each condition a different letter. The control condition was the same as in the first task.

The primary visual cortex was delineated on the individual anatomical images, using an anatomical atlas (Duvernoy) to identify the calcarine sulcus (V1). Primary statistical analysis was restricted to this region of interest (ROI). The fMRI scans were registered to one another and to the anatomical volume, and the time series were subsequently analysed with a multiple regression program (for details see [4]). To avoid detecting activity that is specific for any particular task, and to improve statistical power, a combined task analysis was carried out that focuses on activity that is common to both tasks [4]. For this purpose, scanner data of the two tasks were combined and conjointly analyzed with multiple regression analysis. For the ROI, the number of activated voxels is also reported for the individual tasks.

RESULTS

The significance threshold was set at $T = 3.5$, which corresponds to a p level of 0.05 after Bonferroni correction for multiple comparisons (i.e. number of voxels in the primary visual cortex, V1), to test the null hypothesis that no activity occurred in V1. The fMRI results (Fig. 1a) showed that V1 was significantly activated. Activation of V1 was also observed for both tasks when analysed separately; the number of significantly activated voxels was 7 for the first task and 11 for the second task.

In addition, we examined whole-brain volumes to explore activity in other areas. For this purpose, the statistical threshold was raised to $T = 4.5$ ($p < 0.05$, Bonferonni corrected for the number of voxels in the scanned volume). In addition to activation of the right inferior and middle frontal gyrus and posterior superior temporal gyrus, an extensive pattern of predominantly left hemisphere areas was activated: posterior inferior temporal (PIT) cortex, the parieto-occipital junction, superior temporal and inferior frontal gyrus (corresponding to the areas of Wernicke and Broca, respectively), supramarginal gyrus, dorsolateral prefrontal cortex and precentral gyrus (Fig. 1b).

DISCUSSION

The aim of this study was to test the hypothesis whether V1 would be activated during conscious visual perception without visual stimulation. The question whether primary visual cortex can be activated by internally generated visual material has been previously studied in normal subjects with mental imagery paradigms, but with conflicting results [5–7]. As the experience of synesthesia is more vivid and closer to real perception than the experience of mental imagery, testing the hypothesis of V1 involvement in orthographic color–word synesthesia is of potential interest. Moreover, as synesthesia, in contrast to mental imagery, occurs involuntarily, the results may bear on the neuroanatomy of hallucinations, which can also not be controlled by the experiencer [8].

In the present study, fMRI scanning during performance of two verbal tasks in a subject with color–word synesthesia revealed activation of V1. In normal subjects, performance of such verbal tasks generally does not activate V1 [9,10]. Feedback connections into V1 may play an important role in the integration of information that underlies perception [11]. More specifically, such feedback connections may mediate processes such as perceptual organization, attention and visual awareness [11]. The results of the present experiment provide strong evidence for a role of modulatory feedback connections between associative and primary visual areas in visual experience without direct visual stimulation. The only other neuroimaging study of color–word synesthesia, a PET-study by Paulesu *et al.* [12], failed to find V1 activation, which may be due to methodological differences between PET and current fMRI techniques. The other prominent areas of activation in our study are consistent with the pattern of activation reported by Paulesu *et al.* [12], specifically with regard to PIT cortex and prefrontal activation. The activation of PIT cortex is of particular relevance to the study of color–word synesthesia, as previous studies have demonstrated that this area is involved in the integration of color, shape and language [13].

The findings are consistent with a recently proposed neurobiological theory of synesthesia [8]. These authors advance a neurobiological framework consisting of hierarchical organized cortical sensory pathways. More specifically, they hypothesize that synesthetic experience arises from activity in an inducer pathway (e.g. associated with hearing a word) that propagates through a convergence area into a concurrent pathway (e.g. leading to the experience of seeing color), due to disinhibition of top-down signaling via feedback connections.

We could not determine reliably whether activity was also present in V4, as there are no clear anatomical landmarks for this region. An additional experiment would have to be conducted with a task with colored visual stimuli, to localize V4. To overcome limitations of the present study, future research must also include a normal control group. In addition, it would be interesting to compare patterns of brain activity during color–word

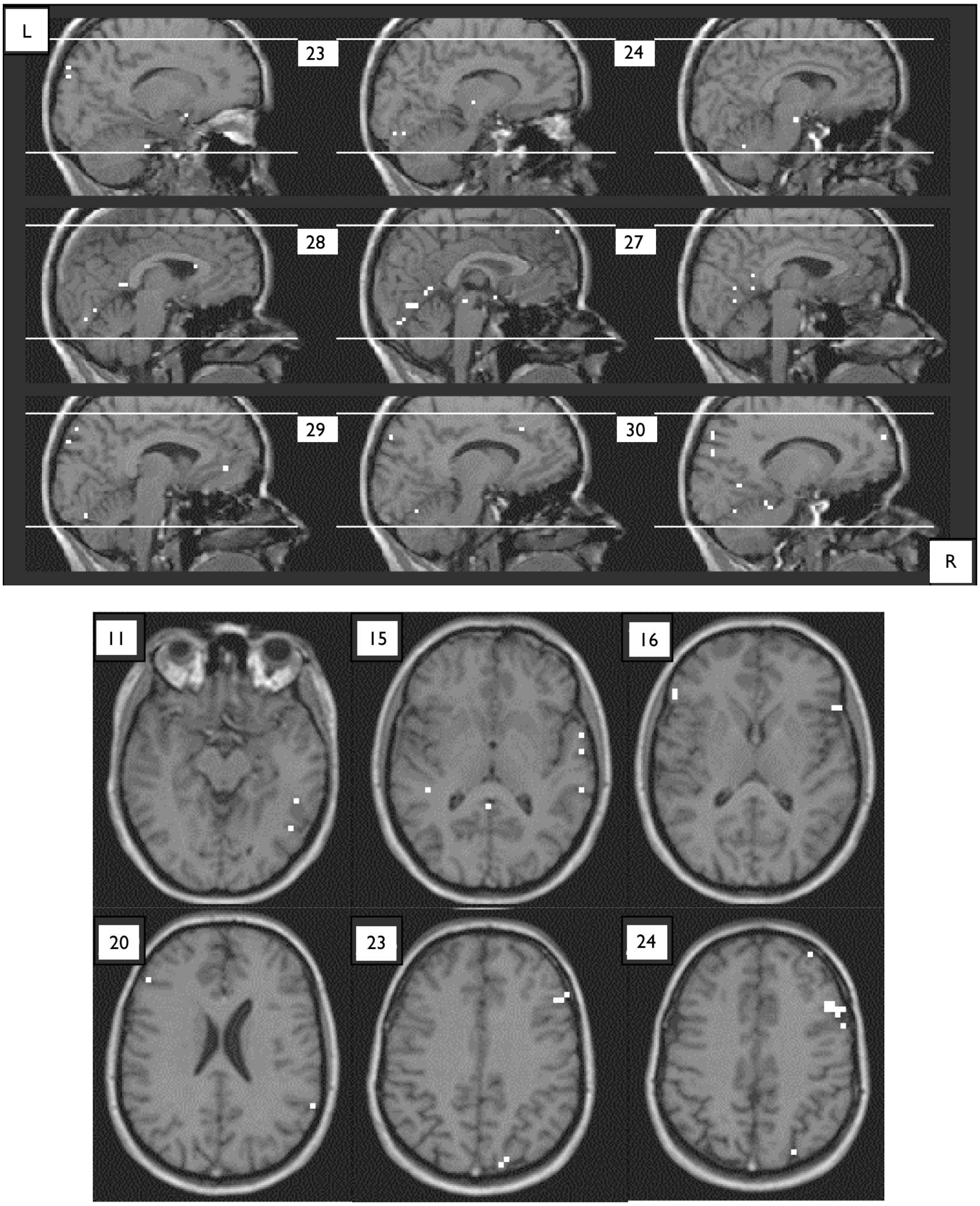

Fig. 1. Areas of activation in a combined analysis of two auditory verbal fMRI tasks in a subject with color–word synesthesia. (**a**) Contiguous sagittal slices (3.5 mm) covering the primary visual cortex V1. White squares represent active voxels at $t > 3.5$ (i.e. $p < 0.05$ corrected for volume of V1), in V1 (and other regions). (**b**) Selected transaxial slices (3.5 mm) displaying activity in language-related regions. Slices are in radiological orientation (left is right and vice versa), White squares represent active voxels at $t > 4.5$ (i.e. $p < 0.05$ corrected for total scanned volume).

synesthesia to activity patterns associated with color–word imagery in normal subjects.

CONCLUSION

Using fMRI we demonstrated that the processing of auditory–verbal material activated V1 in a subject with orthographic color–word synesthesia. Our results indicate that primary visual cortex can be activated by internally generated visual material.

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