The anatomy of conscious vision: an fMRI study of visual hallucinations

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Despite recent advances in functional neuroimaging, the apparently simple question of how and where we see—the neurobiology of visual consciousness—continues to challenge neuroscientists. Without a method to differentiate neural processing specific to consciousness from unconscious afferent sensory signals, the issue has been difficult to resolve experimentally. Here we use functional magnetic resonance imaging (fMRI) to study patients with the Charles Bonnet syndrome, for whom visual perception and sensory input have become dissociated. We found that hallucinations of color, faces, textures and objects correlate with cerebral activity in ventral extrastriate visual cortex, that the content of the hallucinations reflects the functional specializations of the region and that patients who hallucinate have increased ventral extrastriate activity, which persists between hallucinations.

Few imaging studies have investigated the conscious 'pictures' of the external environment that we associate with seeing (visual percepts). The problem that confronts the neuroscientist is recognizing the neural correlate of 'seeing' and differentiating it from afferent sensory activity, which is assumed to remain unconscious[1]. One solution is to study a visual system in which percepts have become dissociated from sensory input. Such dissociation can follow a sudden deterioration in visual abilities in patients who in other respects are neuropsychiatrically normal[2–4]. This syndrome is termed the Charles Bonnet syndrome (named after the Swiss philospher who first described it)[5]. The spontaneous visual percepts (visual hallucinations) experienced by these patients are identical to those associated with normal seeing, although they can be recognized because of their bizarre and often amusing character and because, given the patients' impaired vision, they are seen in greater detail than real stimuli[6]. They differ from visual imagery experiences in that the hallucinations are localized to external space (rather than inside the head), have the vivid qualities of normal seeing and are not under voluntary control. We investigated the neural substrate of visual consciousness in a group of such patients, using two different but complimentary strategies, both of which have proven successful previously[7–9].

The first strategy (Experiment 1) was to ask the patients to signal the onset and offset of each hallucination during a five-minute scan and to then correlate the timing of the hallucinations with the time-course of the fMRI signal. A second, indirect strategy, which did not depend on capturing a hallucination during a scan, identified functionally abnormal brain regions by scanning the patients while they viewed a nonspecific visual stimulus and comparing the results to those of a matched control group who had never experienced hallucinations (Experiment 2).

Results

Visual hallucinations were reported in both experiments. Four patients had spontaneous hallucinations, whereas two others had hallucinations provoked by visual stimulation (Table 1). With the exception of one patient (PP), all hallucinations were in color. Two patients (SH, LC) reported faces, two (FP, PP) reported brickwork, fencing and map textures, and one (AK) reported objects. Unless otherwise stated, all hallucinations occurred in the central visual field. In two patients (AK and FP), Experiment 1 was repeated within the same scanning session to assess response consistency. Three patients (SH, AK, FP) with spontaneous hallucinations were unable to see the stimulus and therefore did not participate in Experiment 2. Therefore, with the exception of one patient (PP), the two experiments had different subjects.

Spontaneous hallucinations

In all four patients with spontaneous hallucinations, the fMRI activity that correlated most significantly with the hallucination report was located in the ventral occipital lobe within or around the fusiform gyrus (Fig. 1). Colored hallucinations were associated with activity in the posterior fusiform gyrus (mean x = +28 and –35, y = –81, z = –13), whereas black-and-white hallucinations were associated with activity behind and above this region (x = 30, y = –84, z = –2). The hallucination of a face was associated with activity in the left middle fusiform gyrus (x = –42, y = –57, z = –7.5), hallucinations of objects were associated with activity in the right middle fusiform gyrus (x = 21, y = –66, z = –18), and hallucinations of textures were associated with activity around the collateral sulcus. In some experiments, additional activity was found outside ventral extrastriate cortex (for example, the frontal activation in patient FP or the activity on the medial occipital lobe in SH, shown in Fig. 1); however, this additional activity was neither consistent between repeated experiments in the same patient nor common among different patients. An increase in fMRI signal often preceded a hallucination (for example, the first, fourth and sixth hallucination shown in Fig. 2a). This temporal relationship was found in all patients studied (Fig. 2b).

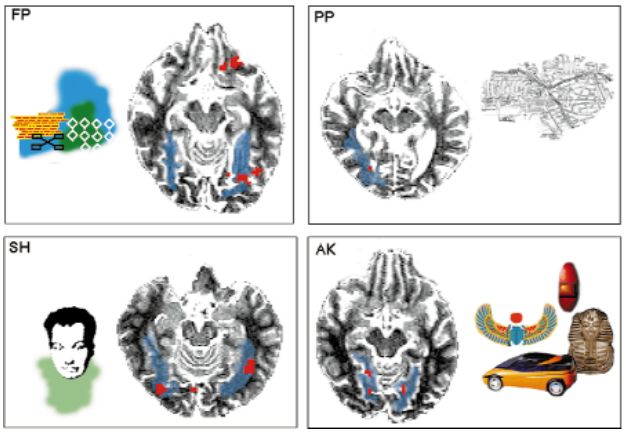

Fig. 1. Spontaneous hallucinations. Positive correlations between T2*-weighted MRI signal and hallucination report are superimposed (red) on transverse sections of high-resolution structural images (r^{max} AK, $p < 1 \times 10^{-3}$; PP, FP, $p < 1 \times 10^{-4}$; SH, $p < 1 \times 10^{-5}$). The fusiform gyrus has been shaded in blue to aid anatomical localization. The hallucinations are illustrated next to each image. Ventral occipital activity was consistent in repeated experiments on the same patient. The r^{max} was always in the ventral occipital lobe, but the optimal temporal shift varied between patients. No areas had a negative correlation at the same level of significance. In all figures, the left of each structural image is the right of the brain.

Response to visual stimulation

In Experiment 2, in patients with impaired vision who had never hallucinated, the visual stimulus evoked activity along the calcarine fissure (area V1), extending onto the ventral surface of the occipital lobe to include the fusiform gyrus (Fig. 3a). In patients with the Charles Bonnet syndrome, this stimulus evoked activity in the striate cortex but failed to do so in the fusiform and lingual gyri (Fig. 3b). We compared the corrected mean level of fMRI signal (see Methods) within the active ventral extrastriate regions in the controls with the cor-

Table 1. The phenomenology and timing of visual hallucinations.

Subject	Diagnosis	Spontaneous hallucination	Number of hallucinations per 5-min scan	Mean duration of hallucinations (s)	Phenomenology
AK	Optic neuritis	Yes	9 ± 2 (3 scans)	16 ± 14	Colored, shiny shapes like futuristic cars or objects found in the pyramids. The shapes contained edges within them and did not look like real objects.
FP	Glaucoma, Retinal detachment	Yes	13 ± 2 (2 scans)	11 ± 6	Brickwork in left upper quadrant of visual field. Fencing in right lower quadrant. Dark blue/green colored ' blob'. Geometrical shape (four squares arranged as the corners of a larger square).
SH	Retinitis pigmentosa	Yes	6	25 ± 24	Face, cartoon-like and in outline. Bright greenish/white light. Vague shadows.
PP	Glaucoma	Yes	5	53 ± 41	Map with lines like roads and an edge like a coast, in black and white. Resembles a page from the A to Z. The names and lettering on the map could not be resolved.
LC	Diabetes mellitus	No	N/A	N/A	The faces and upper body of three soldiers in WW2 uniform against a green background (off-phase of noise stimulus).
SF	Macular degeneration	No	N/A	N/A	Purple raindrops like stars (both phases of noise stimulus). Purple blob that explodes (off-phase of noise stimulus).
CC	Macular degeneration	No	N/A	N/A	No hallucination during scan—Typical hallucination: balls in a net, shrubbery, branches.
PG	Macular degeneration	No	N/A	N/A	No hallucination during scan—Typical hallucination: balls in a net, bumble bee, mouse and large spider moving from left to right.

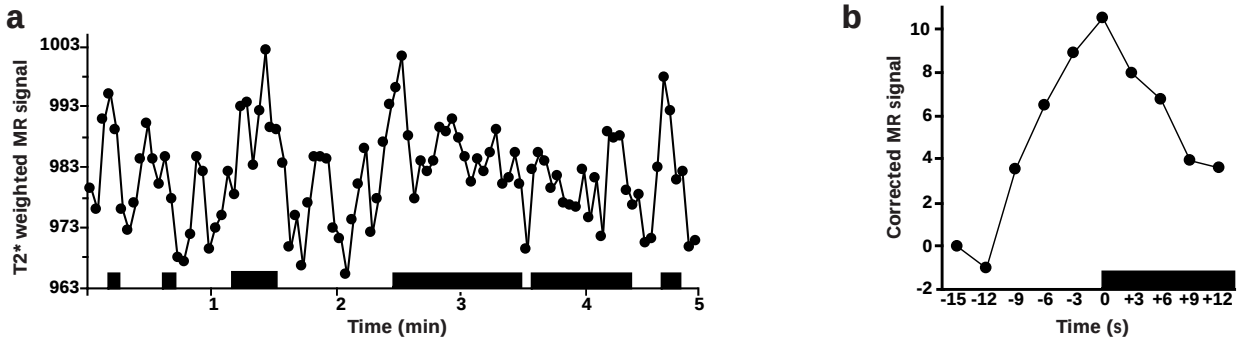

Fig. 2. The timing of visual hallucinations. **(a)** The fMRI time series from the fusiform gyrus (circles) and hallucination log (bars) for patient SH. **(b)** The mean signal intensity in the 12 seconds before and after the report of hallucination onset. Only hallucinations that occurred after a gap of at least 18 seconds have been included to avoid detecting the signal related to the previous hallucination (n = 13). MR signal has been normalized to the –15 s scan. The increase in signal in the 12 seconds preceding a hallucination is significant ($F(4,60) = 3.83$; $p < 0.01$).

responding silent regions in the patients. Mean signal was increased significantly in the hallucinators relative to the controls across the whole five-minute experiment ($t = 2.94$, $df = 8$, $p < 0.025$). The apparent silence of the region was due to a relatively greater increase in signal between the periods of visual stimulation (OFF) than during stimulation (ON), with a consequent degradation of periodic signal (see Methods).

Discussion

Our two sets of results converge on a single conclusion, that hallucinations of color, faces, textures and objects result from increased activity in the ventral occipital lobe. A phasic increase in activity causes a discrete hallucination (Experiment 1), whereas a tonic increase in activity decreases the response to external visual stimulation (Experiment 2). An unexpected finding was the rise in fMRI signal before the onset of the conscious experience, the opposite of the normal delayed response to visual stimulation found in fMRI experiments[10,11]. Patients described the appearance and disappearance of their hallucinations as sudden (< 1 s), all-or-nothing phenomena, so the observed 'reversed' delay is not an artifact of uncertainty as to when to report the experience. One explanation for this finding might be that cerebral activity must exceed a certain threshold level to contribute to visual consciousness[12] and that subthreshold neurophysiological activity starting 15 seconds before the hallucination is responsible for the increase in signal found at –12 seconds.

We found a striking correspondence between the hallucinatory experiences of each patient and the known functional anatomy of the occipital lobe. In patients who hallucinated in color, activity was found in the fusiform gyrus in an area corresponding to the color center, area V4 (mean $x = \pm 28$, $y = -79$, $z = -16$, see refs 13, 14), whereas in the patient who hallucinated in black and white, the activity was outside this region (posterior extent of $y = -82$, max $z = -12$, see ref 14). The descriptions of featureless colors in the hallucinations are similar to the descriptions given by patients whose ventromedial occipital cortex has been stimulated directly[15]. In the patient who hallucinated an unfamiliar face, additional activity was found in the left middle fusiform gyrus, an area that responds to unfamiliar face stimuli (mean $x = -35$, $y = -63$, $z = -10$, see ref 16). In patients who hallucinated brickwork, fences and a map, activity was found around the collateral sulcus, an area that responds to visual textures[11]. Finally, in the patient who hallucinated objects, activity was found in the middle fusiform gyrus, an area that responds to visually presented objects[17,18]. These results are, to our knowledge, the first evidence of a correlation between the location of activity within specialized cortex and the contents of a hallucination.

Visual hallucinations are difficult to dismiss as vivid imagery experiences, as they differ both qualitatively (see Introduction) and, at least for color hallucinations, neurobiologically. (Area V4 was not differentially activated in a color imagery task compared to a spatial-orientation control task[19].) The neural substrate of a color hallucination is thus closer to that of a true (non-hallucinated) percept than that of color imagery. The areas identified are unlikely to be related to the motor signaling response of the patients, as this would occur at twice the hallucination frequency

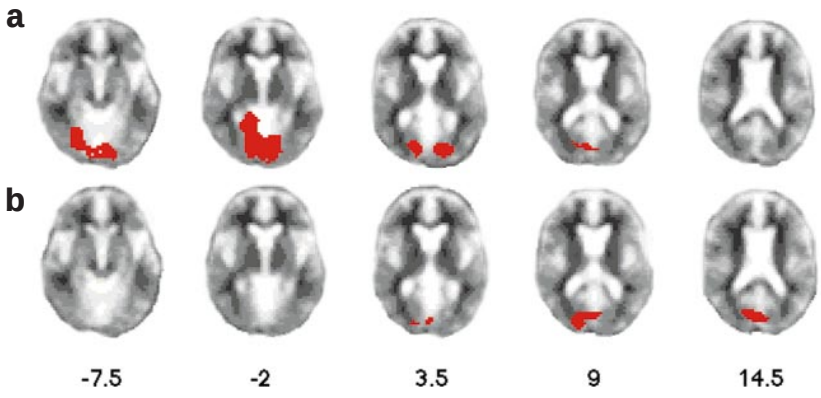

Fig. 3. Generic activation to visual stimulation. Voxels in phase with the stimulus are thresholded at $p < 0.05$, corrected for multiple comparisons, and superimposed (red) on transverse slices of a template structural image. Talairach z coordinates in mm above and below the AC–PC plane are displayed beneath each column. **(a)** Control patients. **(b)** Hallucinators.

(patients signaled both the onset and the offset of each hallucination), and our correlation method would thus be relatively insensitive to it. The complexity of the percepts and the absence of consistent activity in the striate cortex make it unlikely that the ventral occipital lobe is responding to spontaneous discharges in the retina or LGN. Similarly, the absence of consistent activity outside the occipital lobe argues against the hypothesis that activity in the frontal lobe is a prerequisite for conscious vision[1,20] or that visual complexity in hallucinations implies activity in the anteriolateral temporal lobe[15]. However, our data fall short of disproving such theories. If the spatial pattern of 'higher' activity is not fixed for a given perceptual experience or is so diffusely distributed that its activity is not reflected in a change in fMRI signal, it would not have been detected by our method. Visual consciousness is presumably the result of complex neuronal processes with top-down influences. The results presented above suggest that such top-down complexity may be localized within each specialized area rather than being distributed across the brain.

We conclude that in patients who are neuropsychiatrically normal and in the absence of afferent sensory input, conscious percepts of color, texture, faces and objects are associated with activity in the ventral extrastriate cortex reflecting the known functional specializations of the region. Why these particular brains are functionally abnormal and whether the abnormality is common to all patients with visual hallucinations will require further investigation. These results complement previous studies of consciousness for motion[12,21] and support the hypothesis that processing within each specialized visual area makes a direct contribution to conscious vision[22,23].

Methods

PATIENTS AND CONTROLS. Eight patients with the Charles Bonnet syndrome (seven male, one female) were selected from a questionnaire-based study of visual hallucinations at the Institute of Psychiatry. Selection was based on (i) the frequency of stereotyped hallucinations (> 1 per day), (ii) the absence of psychiatric illness, epilepsy or cognitive impairment (MMSE > 25, ref. 24) and (iii) suitability for an MRI scan. Control patients who had never hallucinated (five males), matched for age, acuity and visual field defect, were recruited from Kings College and St Thomas' Hospitals. All patients gave informed consent and were given psychiatric, neurological and ophthalmological assessments.

SPONTANEOUS HALLUCINATIONS. The room lights were dimmed, and patients were asked to signal the onset and offset of each hallucination, which was recorded on a computer linked to a hand-held keypad in the scanner. One patient logged the events himself; the remaining three raised or lowered a finger while the event was logged by an investigator. Descriptions of the hallucinations were collected after each scan.

VISUAL STIMULATION. A visual stimulus, consisting of five one-minute cycles of 30 s of visual noise (ON) followed by 30 s of a black screen (OFF), was back-projected onto a translucent screen placed over the end of the scanner bore (elongated semi-circular field, 13° vertical × 27° horizontal). The stimulus contained luminance, color, motion and form across a range of spatial and temporal frequencies. Patients were asked to attend the stimulus and to describe their hallucinations after each scan. No attempt was made to correct refractive errors.

IMAGE ACQUISITION. Gradient echo, echoplanar images (EPI) were acquired on a 1.5-Tesla GE Signa System (General Electric, Milwaukee) with an Advanced NMR operating console and quadrature birdcage headcoil for radio frequency transmission and reception. In each experiment, 100 T2*-weighted images depicting blood oxygen level-dependent (BOLD) contrast[25] (TR = 3 s; TE = 40 ms) were obtained at each of 14, non-contiguous 7-mm slices (0.7 mm interslice spacing), parallel to the plane passing through the anterior and posterior commissures (AC–PC) and covering the whole brain (in-plane resolution 3 × 3 mm). A high-contrast, high-resolution inversion recovery EPI image (TE = 74 ms; TI = 180 ms; TR = 1600 ms; NEX = 8; voxel size = 1.5 × 1.5 × 3.3 mm) was acquired after the experiments.

IMAGE ANALYSIS. In Experiment 1, the time series were motion corrected[26], smoothed in *x* and *y* (7-mm full width half maximum (FWHM)) and the coefficient of correlation (*r*) was calculated at each voxel. The process was repeated after shifting the hallucination log with respect to the fMRI time series in steps of one scan (shifts of –9 s, –6 s, –3 s, 0 s, +3 s, +6 s, +9 s) to optimize *r* for each patient (r^{max}). Probability maps were calculated from the estimated r^{max} with 100 degrees of freedom and co-registered with the high-resolution structural image. Talairach[27] coordinates were derived from transformed r^{max} images (see below). In Experiment 2, the time series were motion corrected[26], and the observed and randomized (10 permutations) fundamental power quotient (FPQ) at 0.016 Hz was estimated at each voxel[28]. FPQ images were transformed into Talairach space using transformation parameters derived from the structural image[29]. After smoothing in *x* and *y*, (20-mm FWHM), generic activation across patients was computed at each voxel by comparing the median observed FPQ with the median randomized FPQ[29]. Corrections for multiple comparisons were based on the number of independent voxels after smoothing. The phase of activity was calculated from sine and cosine terms in the regression model. The location of generic activation in the original, non-transformed T2*-weighted images was calculated using the transformation parameters derived above. Mean signal within the ventral occipital region of interest over (i) the whole five-minute experiment, (ii) the ON periods and (iii) the OFF periods was corrected for global intersubject differences in maximum signal across the whole slice.

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