Seeing faces: evidence suggesting cortical disinhibition in the genesis of visual hallucinations.

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Abstract

The neural mechanisms responsible for triggering visual hallucinations are poorly understood. Here, we report a unique patient whose hallucinations consist exclusively of faces, and which could be reliably precipitated by looking at trees. Using functional Magnetic Resonance Imaging (fMRI), we found that, while face hallucinations was associated with increased neural activity in a number of cortical regions, including low-level visual areas, there was significant decreased activity in the right fusiform face area, a region that is empirically defined by increase activity during veridical perception of faces. These findings indicate key differences in how hallucinatory and veridical perceptions lead to the same phenomenological experience of seeing faces, and are consistent with the hypothesis that hallucinations may be generated by decreased inhibitory inputs to key cortical regions, in contrast to the excitatory synaptic inputs underlying veridical perception.

Hallucinations are percepts occurring in the absence of real stimuli. They differ from imagery in that the products of the latter are clearly recognized as internal to the observer, whereas hallucinations are located as external, regardless of whether the observer has insight into their relation (or lack thereof) to reality[1].

Visual hallucinations range from vague unformed images to highly detailed experiences that are nearly as vivid as real perception, and may occur in a variety of conditions[2]. They may be due to hypnagogic states and visual sensory deprivation in healthy subjects, visual loss in brain damaged patients, neurologic conditions such as epilepsy, diffuse Lewy body disease and peduncular hallucinosis, or psychiatric conditions such as schizophrenia and substance abuse or withdrawal states[3]. Despite the diversity of pathology, it has been hypothesized that a common neural mechanism for the generation of visual hallucinations is disinhibition of visual cortex, via a 'release phenomenon' secondary to defective function or modulation of thalamocortical relationships[4, 5]. This contrasts significantly with veridical perception, in which feedforward thalamo-cortical and cortico-cortical glutamatergic connections are responsible for relaying information through the visual processing hierarchy[6, 7].

Confirmation of this mechanistic hypothesis is difficult because of the lack of an animal model of hallucinations. Moreover, whether human functional neuroimaging can provide support for this concept is not yet clear. Previous functional Magnetic Resonance Imaging (fMRI) studies have shown increased Blood Oxygen Level-Dependent (BOLD) signal change in many extrastriate and other cortical areas during (and sometimes preceding[8]) hallucinatory episodes, with a suggestion that increased signal may occur in areas directly involved in processing the content of the hallucination[9]. However,

interpreting these results is complicated by the facts that many patients have a wide range of content to their hallucinations, and that the rich interconnectivity between visual areas makes it difficult to distinguish primary from secondary effects cascading through the network.

Here, we examined a man whose hallucinations consisted solely of faces, and which could be produced reliably by staring at trees. This gave us the unique opportunity to determine if the neural activity in face-processing structures differed according to whether the patient was experiencing a veridical or hallucinatory perception of faces. Specifically, we examined the fusiform face area (FFA), a region in the medial occipitotemporal cortex that responds more strongly to faces than to any other object [10-12]. During fMRI, we first used the viewing of facial images to localize the patient's FFA, which then allowed us to determine the BOLD signal change in this pre-eminent face processing region when the patient hallucinated faces while looking at images of trees.

RESULTS

The patient reported face hallucinations during 29 of 60 trials with images of trees. The contrast of the fMRI signal across the whole brain during hallucination and non-hallucination trials revealed increased neural activity in both cortical and subcortical regions, including areas involved in early visual processing (Broadman's areas 17, 18, 19) (Table 1, Fig. 1), consistent with prior neuroimaging studies of visual hallucinations [9, 13].

The functional localizer identified the patient's right FFA in the occipitotemporal cortex (Fig. 2a). We performed a region-of-interest analysis to assess the effect of face

hallucinations on the BOLD signal in the FFA. The contrast revealed a statistically significant decrease in neural activity while the patient was hallucinating faces, compared to trials in which he was not ($t=3.98, p< 0.0001$) (Fig. 2b).

To exclude for the possibility that differences in BOLD signal between hallucination and non-hallucination trials might be due to differences in the tree images, we had a healthy age-matched control subject perform the same fMRI study. We showed the same tree images and contrasted the BOLD signal on the trials in which the patient experienced face hallucinations with the trials in which he did not. Whole brain analyses in the control subject did not reveal any significant difference between the patient's hallucinatory and non-hallucinatory trials. Likewise, after successfully localizing the control subject's right FFA (Fig. 2c), the region-of-interest analysis on this region failed to reveal any significant difference in BOLD signal between the hallucinatory and non-hallucinatory trials ($t=0.58$, $p> 0.05$; Fig. 2d).

DISCUSSION

While our data agree with the majority of studies showing increased BOLD signal change in many visual and non-visual areas during hallucinatory periods[9, 13], they provide the new observation that in a region that is specifically involved in the processing of stimuli corresponding to the content of the hallucination, hallucinations are associated with a *decrease* rather than an increase in BOLD signal.

This finding contrasts with prior reports suggesting that hallucinations might be associated with increased signal in regions specialized for the content of the hallucination. Ffytche and colleagues[14] studied four patients with visual hallucinations

from Charles Bonnet syndrome due to ocular causes of visual loss and found that hallucinations of colour, objects and faces were associated with patterns of increased neural activity that corresponded approximately to known cortical centers for colour, object and face processing. However, this study did not (or possibly could not, given the visual loss) use functional localizers to confirm the location of these cortical centers. Moreover, the content of their patients' hallucinations was variable. The one subject who hallucinated faces also saw bright greenish white light and shadows, with activity posterior to the usual location of the fusiform face area, as the authors acknowledged. In addition, the result reported for this patient with face hallucinations is surprising in that increased activity was found in the left rather than the right fusiform gyrus, contrary to the usual predominance of right-sided activation when healthy subjects view faces[15].

The only study that did use functional localizers examined a patient with schizophrenia and only visual hallucinations at the time of scanning[16]. In visual cortex, activation was limited to early visual areas; however, a region-of-interest analysis was not performed on localized areas. The value of this report for functional correlation is further limited by the range of hallucinatory content of this patient, who reported seeing "family members who had objects in their hands or were sitting on a table or in a known room"[16].

Thus, as in these two other studies, our whole brain analysis revealed increased BOLD signal during hallucinations in posterior visual regions bilaterally (Table 1, Fig. 1a), which in the right hemisphere was indeed posterior to the patient's FFA. However, in this patient with highly stimulus-specific hallucinations, there was decreased BOLD signal in the cortical region most selective for the content of the hallucination, the FFA (Fig. 2b).

This is in sharp distinction with the increased signal associated with veridical face perception in the same region (Fig. 2a), supporting assertions that hallucinations are generated by mechanisms that significantly differ from those operating during veridical perception[17-19].

How can we interpret decreased fMRI BOLD signal during the hallucinatory perception of faces in a cortical face area defined by increased signal during veridical face perception? BOLD signal may reflect a number of different cortical events, including local field potentials related to interneuron activity, neuronal spiking, and significantly, either inhibitory or excitatory synaptic inputs [20-22]. The suggestion that inhibitory input can be correlated with BOLD signal is supported by observations in other cortical regions[23], such as the increase in BOLD signal in the frontal eye field during antisaccades[24], which single cell recordings show to be associated with reduced neural activity (and likely increased inhibitory inputs) in this region[25]. Thus, disinhibition of visual cortex during hallucinations could be reflected in less inhibitory synaptic input and therefore less BOLD signal while they were occurring. This would contrast with the normal increase in BOLD signal in the critical area during veridical perception, in which visual activity is generated by increased excitatory input to that critical area. Furthermore, disinhibition of the FFA could result in increased feedforward and feedback excitatory outputs from the FFA to other visual regions and even more distant areas such as inferior temporal and frontal cortex, which are know to be connected with the occipital cortex via the longitudinal[26] and uncinate[27] fasciculi. This could then account for the increased BOLD signal that we found in other regions (Table 1, Fig. 1): if so, it may also indicate

that the increased BOLD reported in the other studies may have been secondary or indirect cortical effects of the hallucinations[14, 16].

In summary, our results provide evidence that veridical and hallucinatory percepts rely on different neural mechanisms. While other interpretations of the pattern of BOLD signal that we found in this study cannot be excluded, our findings are compatible with a disinhibition account of visual hallucinations. Whether these results can be generalized to other types of hallucinations requires further investigation; nevertheless, disinhibition has been promoted in peduncular hallucinosis, release hallucinations secondary to visual loss, and hallucinations in diffuse Lewy body disease[28-30]. In the latter condition disinhibition has received some support from the finding of occipital hypometabolism[31], although this has not been directly linked to the hallucinatory experience, as in our patient.

METHODS

Case history. A 49-year-old ambidextrous man reported visual hallucinations exclusively of faces (no objects, scenes, or other material) when he stares at trees. The faces are dynamic, unfamiliar and make slightly different expressions but do not talk, confining the hallucinatory experience to the visual domain. The faces differ between episodes and may appear after a few seconds of staring at a tree, in some cases requiring more time. They disappear when gaze shifts. The patient has preserved insight into the falsity of the hallucinations. His vision is otherwise normal and he denies problems recognizing faces. Hallucinations began during a period of LSD use and have continued despite cessation of such use many years prior. He has also been diagnosed with schizoaffective disorder. Repeated EEG assessments and MRI of his brain have been normal. Patient's medications include quetiapine, which has reduced the frequency of hallucinations, as well as carbamazepine, topiramate, olanzapine, and rabeprazole. His visual, mental status and neurological examinations were normal.

Neuropsychological testing showed that the patient's general cognitive level, tested by means of the WAIS-R[32], was within the normal range, with a total IQ of 95. The neuropsychological assessment did not reveal any attentional or mental imagery defect. Memory skills were well preserved in the verbal and episodic domains. In the spatial memory domain he scored normally in the backward version of the Corsi Block Test[32] (10/16) but not in the forward version (8/16). In the recognition domain, performance was reduced for both words and faces (Warrington Recognition Test[33]: words 38/50, faces 36/50). General perceptual abilities were well preserved, as assessed by the Visual Object and Space Perception Battery[34]. For face stimuli, while the patient had some

difficulty with the Benton Face Recognition Test[35] (35/50), his processing of expression and identity in the Florida Affect Battery[36] was normal.

As a control subject for the fMRI experiment, we scanned a matched 48 year-old ambidextrous man with no neurological or psychiatric history, no prior episodes of hallucinations, and no difficulty with face recognition. For both patient and healthy control subject, informed consent was obtained in accordance with the principles of the Declaration of Helsinki, and the protocol was approved by the Institutional Review Boards of the University of British Columbia and the Vancouver General Hospital.

Experimental stimuli. Prior to scanning we showed the patient an array of 150 images of trees, to determine the duration of steady fixation required for a face hallucination to emerge from each image. These durations ranged from 1.6 to 18.7 s. From these images we selected the 30 tree images that produced hallucinations with less than 3 s of viewing, and the 30 images that only produced hallucinations with more than 7 s of viewing. Each image displayed a tree in the centre of the image, without other objects or people.

fMRI data collection. The patient underwent two functional runs, namely the '*localizer'* and the '*tree'* run. During the *localizer* run the patient viewed photographs of non-living objects (e.g. television, basketball) and faces (neutral and expressive) presented in separate blocks. This *functional localizer* is similar to the original one used to identify the fusiform face area (FFA)[12], which is currently used by the majority of the laboratories investigating face processing in humans[15]. During the *localizer* run, participants perform a 'one-back task', in which they are required to press a button if an image was identical to the previous one (i.e. a task that keeps

subjects focusing on the perceptual processing of the stimuli). We asked the patient to perform the same task. The *localizer* run began and ended with a fixation block showing a cross in the centre of an otherwise blank screen. Additional fixation blocks were alternated with image blocks, with each block lasting 12 seconds. Six blocks of each image category (object, neutral face, expressive face) intermixed with fixation block were randomly presented. Each image block consisted of 15 images (12 novel and 3 repeated), all sized to a width of 400 pixels and presented at screen centre for 500ms, with an inter-stimulus-interval (ISI) of 300ms. The duration of the *localizer* run was 444 seconds in total, after which the patient underwent the *tree* run.

During the *tree* run, the patient was presented with the 60 photographs displaying trees. Each trial consisted of one image presented for 6 seconds, followed by a blank screen of the same duration. These 60 trials were randomly intermixed with 30 fixation trials presenting a cross in the centre of the screen (6 s average time). In total, the *tree* run consisted of 90 randomly administered trials that lasted 1800 seconds. The patient was required to press a button as soon as face hallucinations occurred during the presentation of the tree images. This allowed us to classify *a posteriori* trials as hallucination (n=29) and non-hallucination (n=31) ones. After this *tree* run, the patient underwent a 3D structural anatomical scan. The healthy control subject underwent an identical protocol scan including both *localizer* and *tree* runs.

fMRI data processing and analyses

All images were acquired in a 3.0 Tesla Phillips scanner. Stimuli were presented using Presentation 9.81 software and were rear-projected onto a mirror mounted on the head coil. Whole brain anatomical images were acquired using a T1-weighted echoplanar imaging (EPI)

sequence, consisting of 170 axial slices of 1mm thickness (1mm gap) with an in-plane resolution of 1mm X 1mm (FOV=256). T2-weighted functional runs (TR=2s; TE=30ms) were acquired using an interleaved ascending EPI sequence, consisting of 36 axial slices of 3mm thickness (1mm gap) with an in-plane resolution of 1.675mm X 1.675mm. The *localizer* run consisted of 223 functional volumes, while the *tree* run consisted of 540 functional volumes.

The first volume of each functional run was discarded to allow for scanner equilibration. All MRI data were analyzed using BrainVoyager QX Version 1.8 (www.brainvoyager.com). Preprocessing of functional runs consisted of corrections for slice scan time acquisition, head motion (trilinear interpolation), and temporal filtering with a high pass filter in order to remove frequencies less than 3 cycles/time course. The functional runs were co-registered to the patient's anatomical scan, using the first retained functional volume to generate the co-registration matrix. The *localizer* time course was analyzed with a single subject general linear model (GLM), with object (O), neutral (NF) and expressive (EF) faces as predictors. Analysis of NF+EF>2*O was overlaid on the whole brain and significance was set at $p<0.05$, with correction for multiple comparisons (Bonferroni correction). A similar procedure was adopted for the *tree* run, the time course of which was analyzed via a single subject GLM, with hallucinations (H) and non-hallucinations (noH) images as predictors. Analysis of H>noH was overlaid on the whole brain and significance was set at $p<0.05$, with correction for multiple comparisons (Bonferroni correction). Finally, we performed a Region of Interest Analysis (corrected for multiple comparisons) in which we contrasted the hallucinations and the non-hallucinations images within the fusiform face area (FFA) detected in the *localizer* run. Identical analyses were performed on the functional data collected in the healthy control subject.

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Competing Interests Statement

The authors declare that they have no competing financial interests.

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Figure 1. Neural activity during hallucinations. Horizontal view of the neural activity detected, while the patient experienced visual hallucinations (whole brain analysis, hallucinations minus non-hallucinations trials), in (a) the right and left visual areas (see Table 1 for Talairach coordinates), (b) left premotor region (X=-48; Y= -13; Z= 31; peak *t*-value= 6.06), (c) left middle/inferior temporal gyrus (X=-39; Y= -17; Z= -14; peak *t*-value= 5.86), and (d) right inferior frontal (X=37; Y= 40; Z= 12; peak *t*-value= 6.29) and middle temporal (X=47; Y= -71; Z= 15; peak *t*-value= 6.41) gyri.

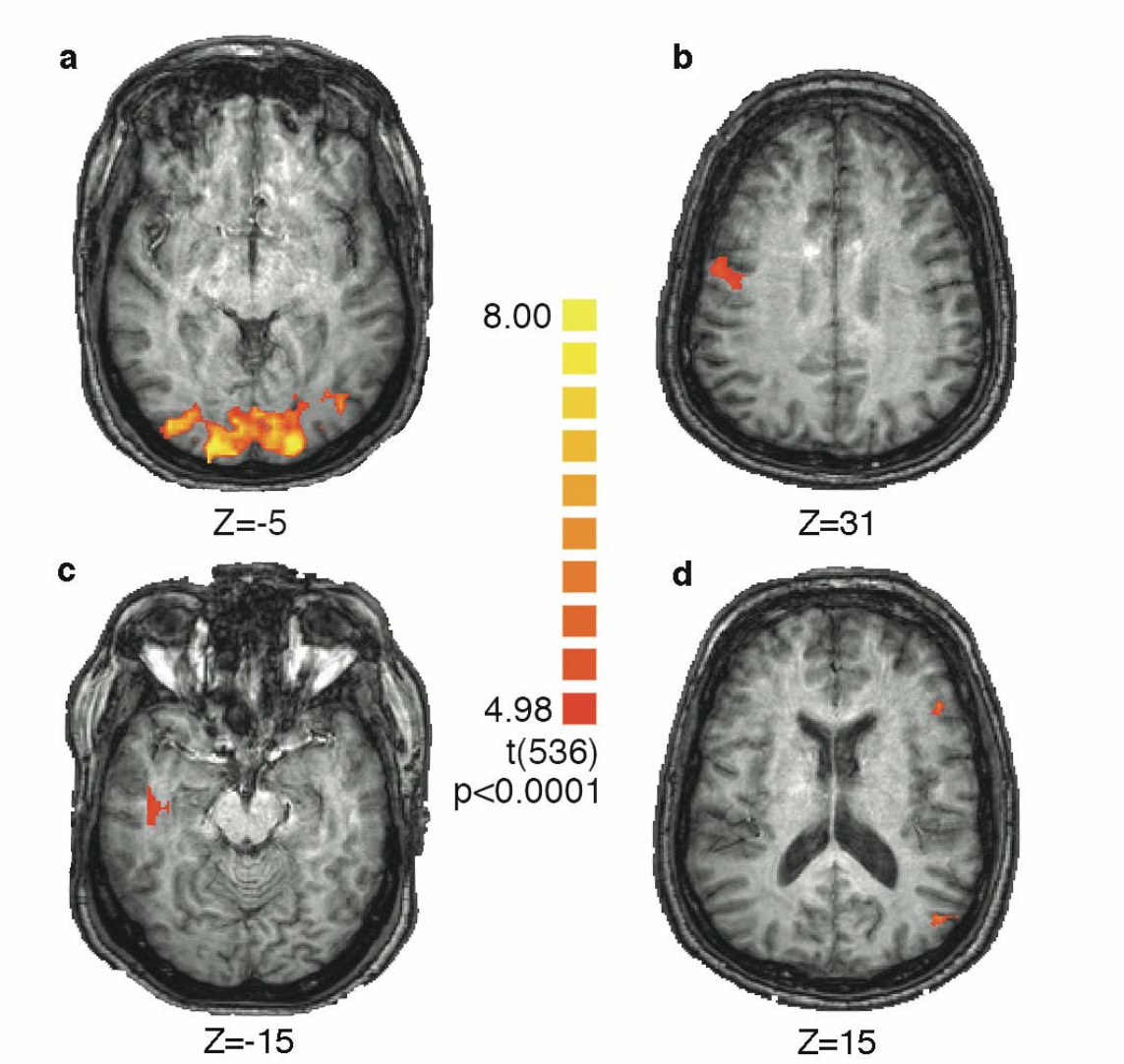

Figure 2. Fusiform face area and BOLD signal change. Horizontal view of right FFA as identified by the functional localizer in (a) patient (X=38; Y= -45; Z= -22; peak *t*-value= 5.31) and (c) control (X=33; Y= -49; Z= -18; peak *t*-value= 9.93). The histograms display the BOLD signal change detected in the right FFA during hallucinations and non-hallucinations trials in both patient (b) and control (d).

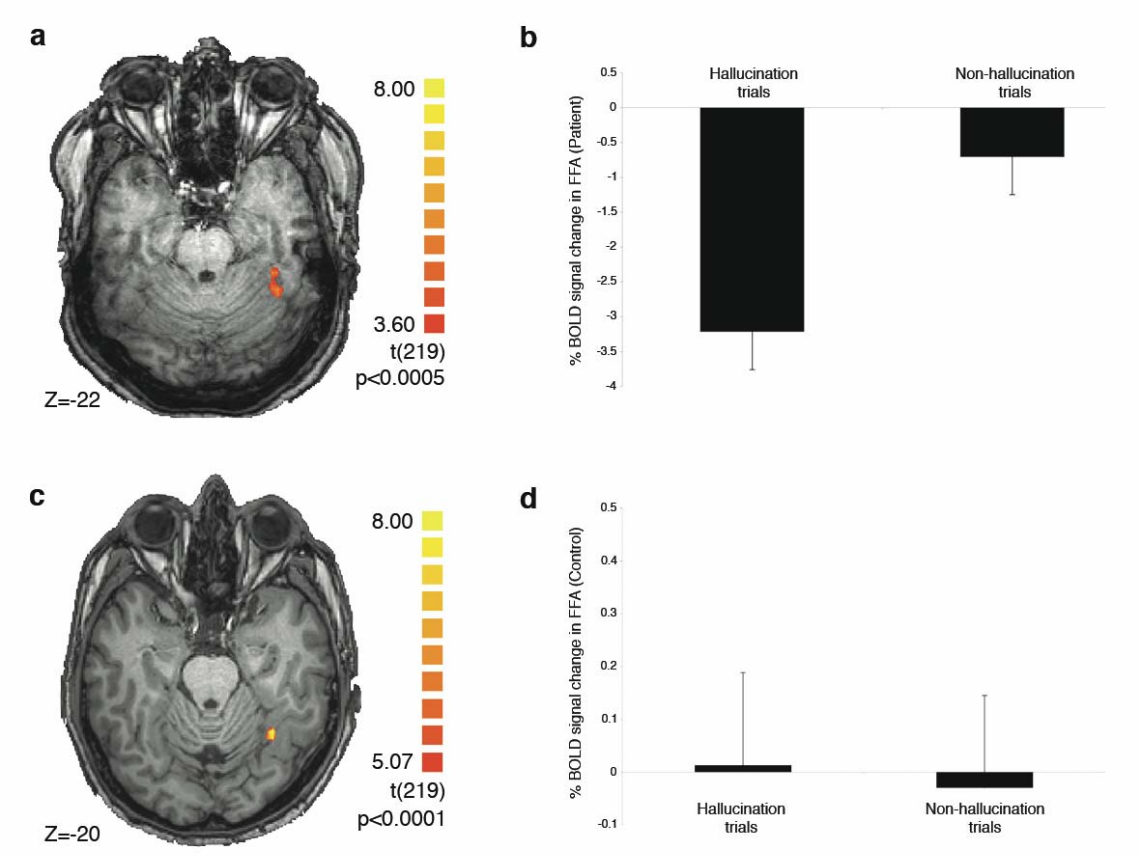

Table 1. Neural activity detected across the whole brain while the patient experienced face hallucinations (hallucination minus non-hallucination trials).

Anatomical Region (Brodmann Area)	Talairach coordinates (X, Y, Z)			Peak *t*-value	Number of Voxels
Right Inferior Frontal Gyrus (46)	37	40	12	6.29	51
Right Superior Temporal Gyrus (39)	50	-62	29	6.23	83
Right Middle Temporal Gyrus (39)	47	-71	15	6.41	128
Right Precuneus (7)	10	-62	30	5.94	100
Right Occipital Gyrus (19)	48	-70	-15	6.25	217
Right Fusiform Gyrus (18)	25	-89	-9	6.76	1016
Right Pontis-parahippocampus	24	-31	-19	6.52	943
Right Caudate Nucleus	15	15	4	5.51	63
Right & Left Calcarine/Lingual gyrus (17/18)	-5	-83	-7	6.84	740
Right Cerebellum	41	-62	-29	6.92	295
Left Premotor (4/6)	-31	-13	-56	6.13	92
Left Premotor (4)	-48	-13	31	6.06	228
Left Superior Parietal Lobe (7)	-5	-58	53	6.18	96
Left Superior Temporal Gyrus (22)	-54	-49	20	6.17	66
Left Middle Inferior Temporal Gyrus (20/21)	-39	-17	-14	5.86	647
Left Fusiform Gyrus (19)	-27	-67	-16	6.11	50
Left Caudate Nucleus	-15	16	5	5.52	78
Left Cerebellum	-17	-72	-29	6.03	59
Left Pontis	-5	-30	-19	5.44	88
Left Cerebellum (extending to parahippocampal cortex and hippocampus)	-22	-37	-12	6.42	1870