

Unconscious activation of visual cortex in the damaged right hemisphere of a parietal patient with extinction

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Summary

Visual extinction is a sign classically associated with right parietal damage. The patient can see a single stimulus presented in the ipsilesional or contralesional visual field, but is characteristically unaware of the same contralesional stimulus during simultaneous stimulation of both fields. The ipsilesional stimulus is said to ‘extinguish’ the contralesional stimulus from awareness during bilateral stimulation, perhaps due to a pathological bias in attention towards the ipsilesional side. Recent psychophysical evidence suggests that, although extinguished stimuli are not consciously seen, they may undergo residual processing and exert implicit effects on performance. However, the neural structures mediating such residual processing for extinguished stimuli remain unknown. Here we studied the neural activity evoked by an extinguished visual stimulus, using event-related functional MRI (fMRI), in a patient with circumscribed right inferior parietal damage and profound left-sided extinction. Monochrome objects (faces or houses) were presented in

the left or right field, either unilaterally or bilaterally on each trial, with the patient indicating by button press whether he saw an object on the left, the right or on both sides. He usually saw only the right object on bilateral trials, yet the fMRI data showed activation of visual cortex contralateral to the extinguished left stimulus on these trials (compared with right-only stimulation), in both striate and early extrastriate areas of the right hemisphere. This activity had a similar location and time-course to that resulting from a single stimulus in the left versus right visual field. Cortical pathways involved in the normal processing of a single seen stimulus can thus still be activated by an unseen, extinguished stimulus after right parietal damage. Comparison of fMRI responses for faces versus houses revealed some category-specific activation for extinguished stimuli in right fusiform regions, but only at low statistical threshold. These results are discussed in terms of theoretical accounts for parietal extinction and, more generally, for the neural substrates of visual awareness.

Keywords: neglect; extinction; parietal lobe; attention; fMRI

Abbreviation: blood oxygenation level dependent (BOLD)

Introduction

Visual extinction is a relatively common sign after unilateral brain injury. It can be observed in some form after various brain lesions (Vallar *et al.*, 1994), but is classically associated with right parietal damage (Heilman *et al.*, 1993), when it frequently manifests as one component of the visuospatial neglect syndrome (Vallar, 1993; Rafal, 1994; Heilman *et al.*, 1997). In cases with visual extinction, awareness for single

stimuli, presented to either the left or right visual field, is apparently normal. However, a deficit in awareness emerges when stimuli are presented on both sides simultaneously. Right-hemisphere patients with extinction then typically fail to report awareness of the contralesional (left) stimulus; this appears to be ‘extinguished’ from visual awareness by the competing ipsilesional stimulus.

Several accounts have been proposed for extinction (e.g. Kinsbourne, 1993; Desimone and Duncan, 1995). Currently, the most popular view (for review, see Driver *et al.*, 1997) is that it represents a pathological bias in attention, favouring the ipsilesional side in situations where two or more concurrent stimuli must compete to attract attention. Until now, the neural fate of extinguished stimuli has not been conclusively established, although psychophysical studies have provided some evidence that they can undergo a degree of residual but unconscious processing. For example, latency to detect an ipsilesional (right) visual stimulus can be speeded by a simultaneous contralateral event, even when the latter escapes awareness (Marzi *et al.*, 1996; Smania *et al.*, 1998). Moreover, further studies have shown that various low-level grouping processes may still take place between concurrent events in the two fields of extinction patients (Mattingley *et al.*, 1997). Finally, indirect psychological measures of priming or interference have indicated that various visual attributes, such as colour (Baylis *et al.*, 1993) or form (Audet *et al.*, 1991; Cohen *et al.*, 1995), may still be extracted for extinguished stimuli. In some cases these properties may even include the identity or semantics of an extinguished contralateral object (e.g. Berti and Rizzolatti, 1992; McGlinchey-Berroth *et al.*, 1993; for review, see Driver, 1996).

The neural basis for this residual processing of extinguished stimuli has yet to be established. The issue is similar, in some respects, to that arising for apparently unconscious processing in patients with 'blindsight' (Poppel *et al.*, 1973; Weiskrantz *et al.*, 1974; Zeki and Ffytche, 1998), but there are some important differences. Whereas blindsight patients have scotomas after damage to striate cortex, some extinction patients have no contralateral visual field cut whatsoever and early cortical visual areas (striate and extrastriate) may be structurally intact. It has been proposed that processing in these early cortical areas may still proceed relatively normally for extinguished stimuli and perhaps even continue through to ventral inferotemporal areas that process object identity (Driver, 1996; Driver *et al.*, 1997). According to such a hypothesis, parietal damage may compromise spatial awareness and spatial responding, rather than disrupting early visual processing. However, such proposals remain speculative because, to date, they have been based largely on indirect arguments from behavioural measures rather than direct measures of neural activity in relation to an extinguished stimulus. It remains possible that residual processing in parietal extinction does not rely on the usual cortical pathways for contralateral visual stimuli, but might involve brain regions in the intact hemisphere ipsilateral to the extinguished stimulus and/or subcortical pathways that bypass contralateral striate and extrastriate cortex. Given the many recent controversies concerning whether striate cortex plays a critical role in visual awareness (Weiskrantz, 1986; Barbur *et al.*, 1993; Crick and Koch, 1995; Stoerig and Cowey, 1997; Zeki and Bartels, 1998), it is of particular interest to determine whether this region can still be activated

by an extinguished stimulus after a parietal lesion that structurally spares the geniculostriate projection.

Several previous studies have examined the neural response to visual stimuli in patients with visual neglect after extensive right-hemisphere damage, using visual evoked potentials recorded at the scalp. However, the results have been mixed, with some studies suggesting that scalp potentials for left visual field stimuli can be relatively normal (Vallar *et al.*, 1991; Viggiano *et al.*, 1995), while others suggest an impairment (Angelelli *et al.*, 1996; Angelelli and Spinelli, 1999). Most of these studies presented only unilateral stimulation, not the bilateral stimulation that is essential for eliciting the deficient visual awareness in cases of visual extinction. We discuss later a few event-related potential (ERP) studies of extinction, which have recently appeared in conference-abstract form.

Here we used event-related functional MRI (fMRI) to study the neural fate of extinguished visual stimuli in a single case with right parietal damage. This patient was selected because he exhibited particularly marked visual extinction, following a focal lesion to the right inferior parietal lobe, the area classically associated with extinction and neglect (Vallar and Perani, 1986; Heilman *et al.*, 1993). He showed good detection of unilateral left visual field stimuli, yet pronounced extinction on bilateral simultaneous stimulation, even when large meaningful objects were used (which should presumably be capable, in principle, of generating a substantial neural response in the visual system). This case therefore seemed ideal for testing the neural fate of extinguished stimuli. We were particularly interested in any striate or extrastriate activations that an extinguished stimulus might produce in the damaged hemisphere. We also examined any category-specific activation that extinguished stimuli might produce within inferotemporal regions, given recent theoretical proposals that ventral object-categorization may be relatively preserved in parietal extinction (e.g. Driver, 1996; Driver and Mattingley, 1998). Specifically, we tested for differential brain responses to lateralized pictures of faces compared with pictures of houses, building on previous work that has shown face-specific responses in the fusiform gyrus for normal subjects (Puce *et al.*, 1995; Kanwisher *et al.*, 1997).

Methods

Case report

The patient, G.K., is a 68-year-old man who was taken to hospital because his friends thought he had become acutely confused. On examination he was agitated. There was no weakness or primary disturbance of sensation in his limbs. He did not have a visual field defect or gaze palsy. However, he tended to orient his eyes and head to the right and neglect people to his left. Subsequent testing showed he had left visual and tactile extinction. A CT scan performed 18 h after onset of his symptoms demonstrated a low attenuation area in the right parietal lobe, consistent with infarction. When

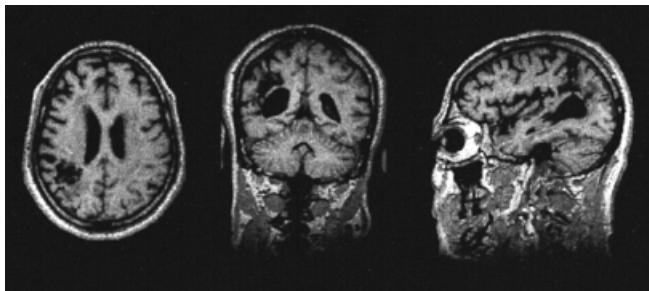


Fig. 1 Anatomical location of lesion. Three sections (axial, coronal and sagittal) are shown through G.K.'s T₁-weighted MRI. A low attenuation area within the right inferior parietal lobule, consistent with an old cerebral infarction, is shown. Note the highly circumscribed nature of the lesion, sparing visual cortex structurally.

tested on the following day, he demonstrated left visual neglect on line bisection, erring a mean of 5.1 cm to the right of the true midline on three 18 cm horizontal lines. On pen-and-paper cancellation tasks he neglected targets on the left. On the Mesulam shape cancellation task (Mesulam, 1985) he cancelled 17 of 30 targets on the right and 0 of 30 on the left.

One year following stroke, G.K. still continued to display left visual extinction and neglect on clinical testing, cancelling 32 of 60 targets (all on the right) on the Mesulam shape cancellation task (Mesulam, 1985) and scoring 87 out of 146 on the conventional sub-tests of the Behavioural Inattention Test (Wilson *et al.*, 1987). The investigations reported here were performed 15 months following stroke, at which time G.K. was fully ambulant and living in the community. Structural MRI demonstrated an area of infarction confined largely to the right inferior parietal lobule (Fig. 1). Lesions in this area are known to be associated with left neglect (Vallar and Perani, 1986) and extinction (Driver and Mattingley, 1998). At the time of the functional imaging session he continued to show reliable left visual extinction and neglect; visual fields were full to confrontation and there were no other neurological abnormalities.

G.K. gave his informed consent to participate in this study, which was approved by the Institute of Neurology, University College, London Ethics Committee.

Functional imaging experiment

There were two phases to the functional imaging experiment. The first phase presented unilateral or bilateral stimulation on different trials, in a random sequence using an event-related fMRI design. G.K. indicated by button press whether he saw an object on the left, the right or on both sides, for each trial. Perceptual reports of a right object only for bilateral stimulation would provide the critical 'extinction' trials. Each object that was presented could be a picture of a face or a house, for the reasons given below. Brief and peripheral stimulation was used, with the aim of producing reliable extinction in the patient. Note that this differs from

many standard fMRI designs for studying visual activations, which typically use long-duration near-foveal stimuli, often within blocked designs.

The second phase did use a blocked fMRI design and was intended to provide an independent localization of any brain region showing a differential response to pictures of faces versus houses (Kanwisher *et al.*, 1997). Specifically, this 'face localizer' phase defined a region of interest responding more strongly to faces than to houses, which we could then interrogate for any similar category-specific responses during the separate event-related phase of functional imaging where we measured extinction. Different blocks in the face localizer phase presented a series of faces or of houses, centred at fixation. The comparison of such blocks has reliably revealed face-responsive areas around the fusiform gyrus in many previous functional imaging experiments with normal observers (e.g. Puce *et al.*, 1995; Kanwisher *et al.*, 1997). These areas are located anterior to retinotopically mapped regions of cortex (Halgren *et al.*, 1999) and respond in normal subjects to both foveal and peripherally presented faces (Wojciulik *et al.*, 1998).

Event-related extinction study

Visual stimuli were presented to the subject on a small screen viewed by a mirror mounted on the head coil. Each trial consisted of the brief presentation, for 150 ms, of a visual stimulus to either the right visual field, the left visual field or to both. Each stimulus was a grey-scale image of a human face or a house, shown in frontal view (these stimuli were taken from Kanwisher *et al.*, 1997). Each subtended $\sim 10 \times 10^\circ$ and was centred $\sim 10^\circ$ from a small central fixation cross. G.K. was asked to indicate on each trial, by button-press with the thumb, index or second finger of his right hand, whether he saw bilateral, left unilateral or right unilateral stimulation, respectively. Six different trial types (conditions) were evaluated: (1) right face; (2) left face; (3) right house; (4) left house; (5) left face plus right house (bilateral); (6) right face plus left house (bilateral).

We did not use all possible combinations of bilateral stimuli (i.e. we never presented two faces bilaterally, nor two houses). Instead, we sought to maximize experimental power by ensuring as many replications as possible of those trial types needed for the critical comparisons. Bilateral trials presenting different categories on each side were most useful for testing any category-specific response to extinguished left stimuli, when compared with right unilateral conditions.

The inter-trial interval was 9.1 s, during which G.K. was asked to fixate the central fixation cross (he was repeatedly reminded of this requirement between successive runs of 30 trials). This inter-trial interval was a non-integer multiple of the scanning time, chosen to ensure that each slice of the image volume sampled the haemodynamic response to individual trials evenly. Five hundred milliseconds before each trial onset, the central fixation cross changed from a small cross to a slightly larger cross in order to alert G.K.

to an impending trial and encourage central fixation. The order of presentation of the six different trial types was randomly intermingled. During the experiment as a whole, 30 repetitions of each different trial type were evaluated to give a total of 180 trials.

Blocked face localizer

Larger grey-scale images of faces or houses, each subtending $\sim 16 \times 16^\circ$, were presented in succession at fixation, each for 800 ms with a stimulus onset asynchrony of 1000 ms. Stimulation epochs lasting 33.6 s (12 image volumes), during which a series of face stimuli or house stimuli were presented, alternated with rest epochs of half that duration, where only the fixation cross was shown. No response was required from G.K., who simply viewed these stimulus streams passively.

Scanning and data analysis

A Siemens VISION system operating at 2 T was used to acquire blood oxygenation level dependent (BOLD) image volumes of 32 contiguous 3 mm slices with an in-plane resolution of 3×3 mm and repetition time of 2800 ms. For the event-related extinction study, scanning took place in six runs of 104 volumes. For the blocked face localizer, there was one run of 150 image volumes. The first six scans of each run were discarded to allow for T_1 equilibration effects. A T_1 -weighted anatomical image was acquired at the beginning of the session.

SPM99 (Wellcome Department of Cognitive Neurology, London: <http://www.fil.ion.ucl.ac.uk/spm>) was used for fMRI data analysis. Each image volume was realigned to the first and spatially normalized to the space of Talairach and Tournoux (Talairach and Tournoux, 1988; Friston *et al.*, 1995a). A custom normalization was performed, with extensive inspection of the normalized image volumes with respect to the normalization template, to ensure image fidelity and check that no distortions were produced by the lesion. The resultant image volumes were then spatially smoothed with a Gaussian kernel of 6 mm full-width half-maximum prior to statistical analysis.

Voxels activated by the visual stimuli were identified by means of a statistical model containing several components. These represented the transient responses produced by the visual stimuli in each condition, together with boxcar waveforms that modelled and removed any run-specific differences in mean evoked activity (Friston *et al.*, 1995b). The event-related changes in evoked activity were modelled by convolving an empirically derived haemodynamic impulse response function with trains of unitary events that were aligned on the presentation times of the visual stimuli (Friston *et al.*, 1998). As each slice in the image volume was acquired asynchronously in a descending fashion, a constant offset was applied to each event train in order to optimize sensitivity in visual cortex. Trials where G.K. made an incorrect response were modelled separately from those trials where he

responded correctly. In addition, high-pass filtering removed low frequency drifts in signal, and global changes in activity were removed by proportional scaling. Each component of the model served as a regressor in a multiple regression analysis. The resultant parameter estimates for each regressor at each voxel were compared using *t*-tests to determine whether significant activation due to a comparison of conditions had occurred. Statistical results given are based on a single-voxel *t*-threshold of 3.12 (corresponding to $P < 0.001$, uncorrected for multiple comparisons), unless otherwise stated. We made no further correction for multiple comparisons within striate and extrastriate areas, for which we had a priori hypotheses. Outside these areas a correction was made for multiple comparisons across the whole brain volume, as we had no prior hypothesis for non-visual areas.

Results

Blocked face localizer

Comparing the evoked responses for epochs where images of faces alone were presented, with those where houses alone were presented, provides a standard measure of face-selective processing (Puce *et al.*, 1995; Kanwisher *et al.*, 1997). This comparison revealed significant activation in the left fusiform gyrus [coordinates $(-32, -64, -18)$, $t = 5.10$; extending forward to $(-34, -48, -20)$, $t = 4.47$] and a homologous area in the right fusiform gyrus [$(40, -60, -20)$, $t = 3.50$; and $(38, -46, -22)$, $t = 4.04$]. These foci are highly consistent with areas in the fusiform gyrus that have previously been reported to show activity that is specific for face stimuli in normal subjects (Kanwisher *et al.*, 1997). The present results are the first to show that such activation can still be observed after right parietal injury. In addition to these large fusiform activations, two small foci of differential activation to faces were seen in left inferior occipital gyrus [$(-48, -78, -2)$, $t = 4.61$; and $(-34, -90, -4)$, $t = 3.65$].

Event-related extinction study

G.K. correctly reported 58 of 60 and 59 of 60 of the unilateral visual stimuli presented in isolation within left or right visual fields, respectively. The good performance for left targets shows that his left neglect did not compromise detection of the unilateral targets used. However, performance was dramatically worse when the same stimuli were presented bilaterally. G.K. correctly identified only two of 60 of these stimuli as bilateral, reporting the remaining 58 of 60 incorrectly as right unilateral trials. Thus, G.K. showed profound visual extinction under our conditions of bilateral stimulation.

Stimulus-specific activation of cortical areas was revealed by statistical comparisons among the event-related experimental conditions. As the baseline (during the inter-trial interval) and fixation stimulation was the same in each

Table 1 Coordinates and t-values for event-related activation

Cortical area	Talairach coordinates			t-value
	x	y	z	
Extinguished bilateral > unilateral right				
Right striate cortex	14	-86	0	4.07
Right posterior fusiform/lingual gyrus	20	-80	-16	4.97
Right lingual gyrus	30	-58	4	3.73
Left lingual gyrus	-14	-84	-12	3.63
Right posterior fusiform gyrus	26	-90	-4	3.60
Right inferior occipital gyrus	24	-96	8	3.19
Right inferior occipital gyrus	50	-76	-8	3.54
Unilateral left > unilateral right				
Right striate cortex	12	-92	4	4.65
Right striate cortex	14	-84	0	4.33
Right posterior fusiform/lingual gyrus	14	-80	-12	4.50
Right fusiform gyrus	18	-64	-2	3.48
Right fusiform gyrus	18	-62	-12	3.86
Unilateral right > unilateral left				
Left fusiform gyrus	-26	-74	-16	3.96
Left fusiform gyrus	-24	-66	-4	3.24
Left middle occipital gyrus	-20	-96	20	4.36
Left posterior fusiform gyrus	-46	-84	-8	3.65
Left posterior fusiform gyrus	-40	-84	-2	3.32

Shown in the table are loci where differential event-related activity was greater during the comparisons of: extinguished bilateral stimulus presentation minus unilateral right visual field presentation; unilateral left minus unilateral right stimulation; or unilateral right minus unilateral left stimulation. The coordinates indicate the maxima of activation (threshold at $P < 0.001$, uncorrected for multiple comparisons).

condition, differential effects should reflect only changes in the peripheral stimulation presented to each visual field.

Activations due to an extinguished stimulus

We compared bilateral trials showing extinction (report of right only) with correctly reported right unilateral trials (i.e. also receiving the report of right only). This corresponds to conditions (5 + 6) - (1 + 3), with those few trials having a response unlike that required for our comparison (i.e. three trials in total) being excluded. Given that G.K.'s response was identical for the conditions we compared here (indicating that he saw only a right visual field stimulus), any differences in cortical activity presumably reflect unconscious processing of the extinguished stimulus in the left visual field.

Several different foci of differential activation were seen, all but one located in visual cortex of the right hemisphere (Table 1). The largest and most reliable foci of activation were located in right striate cortex [maximal coordinates (14, -86, 0)] and early extrastriate right cortex [coordinates (20, -80, -16)]. The location of the striate activation within the lateral aspect of the mid-calcarine fissure was confirmed by direct examination of the T_2 -weighted functional images (which contain some anatomical detail) and by superimposition of the activation on the subject's T_1 -anatomical

image (Fig. 2). The time-courses of activation in the right striate and extrastriate maxima, and the relative level of activation in other relevant experimental conditions, are shown in Fig. 3. The activation of right striate and extrastriate cortex by an extinguished left visual field stimulus suggests a response in contralateral retinotopic cortex, consistent with the lateral localization of the activation in the calcarine fissure. This hypothesis can be further assessed by examining the activations for unilateral stimuli.

Activations due to side of unilateral stimulation

The comparison of left visual field stimulation (conditions 2 and 4, for trials with a correct response) minus right visual field stimulation (conditions 1 and 3, with a correct response) revealed several areas of activation, all located in right visual cortex (Table 1). The largest and most reliable foci of activation were again in primary visual cortex [coordinates (12, -92, 4), $t = 4.65$; extending to (14, -84, 0), $t = 3.48$] and an area of early extrastriate cortex [maximal coordinates (14, -80, -12), $t = 4.50$] (see Table 1 and Fig. 2). Both of these areas overlapped extensively with the activations reported above for the comparison of extinguished bilateral trials versus unilateral right trials (see Fig. 2). This adds further support to the proposal that the activations for extinguished stimuli arose in retinotopic cortex.

Finally, the inverse comparison of right visual field stimulation (conditions 1 and 3) minus left visual field stimulation (conditions 2 and 4) revealed areas of activation located exclusively in left extrastriate cortex (Table 1). Several of these were in locations homologous to those areas activated in the right hemisphere (either by left unilateral stimulation or by the extinguished stimulus on bilateral trials). Qualitatively, the activations for right visual field minus left showed somewhat lower statistical reliability and smaller spatial extent, than those for the inverse comparison.

Searching for category-specific responses to an extinguished stimulus

The different combinations of face and house stimuli in the experimental conditions allow tests for two types of differential effects related to stimulus category. In the first set of comparisons, activation produced by unilateral face stimuli was compared with unilateral house stimuli. At the overall statistical threshold of $P < 0.001$, there was no differential activation to unilateral face stimuli in either visual field. For completeness, we examined the data at lower threshold, within just those areas that had been activated by the foveal face localizer, in the separate blocked phase of functional imaging. This face localizer defined a region of interest for any category-specific effects, from an independent data set. P -values for any category-specific effects in the event-related experiment were corrected for the small volume examined (i.e. the region of interest), using a sphere of 6 mm

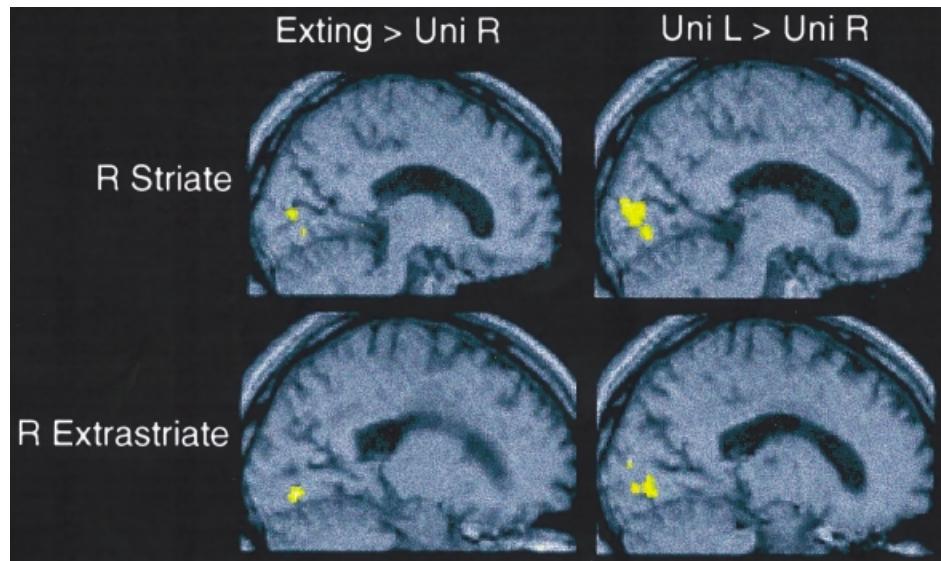


Fig. 2 Areas activated by consciously seen unilateral stimuli in the left visual field and by extinguished left visual field stimuli on bilateral trials. These panels show the location of the largest and most reliable activations, revealed either by the comparison of bilateral trials (showing extinction) minus unilateral right trials (*left panels*), or by the comparison of unilateral left trials minus unilateral right trials (*right panels*). The *x*-coordinate for the slice shown was determined by the peak activation of the comparison it depicts. Details of full coordinates and *t*-values are shown in Table 1. The *upper panels* show loci of activation in striate cortex; the *lower panels* those in the early extrastriate area. All activations are superimposed on the T₁-weighted anatomical image of G.K.'s brain. The similar location of activations for the two contrasts is evident.

radius centred on the loci defined by the face localizer in the fusiform gyrus (reported above) as a basis for this correction. Some differential activation to right unilateral faces (compared with right unilateral houses) was seen in an area overlapping with the anterior left fusiform face area identified in the face localizer [coordinates (-34, -52, -20), $t = 2.62$, $P < 0.01$ uncorrected, $P < 0.05$ corrected for the small volume examined].

Finally, we compared the pattern of activity produced by an extinguished face stimulus with that produced by an extinguished house stimulus. Extinguished faces (condition 5–3) produced some activation in the right fusiform [maximal coordinates (34, -42, -26), $t = 3.42$, $P < 0.001$ uncorrected, $P < 0.05$ corrected for the small volume examined], whereas extinguished houses (condition 6–1) did not produce any activation in the region of interest even at lowered threshold. The interaction indicating differential activation specific to an extinguished face [i.e. conditions (5–3) > (6–1)] showed low-threshold activation [coordinates (34, -46, -24), $t = 2.66$, $P < 0.01$ uncorrected, $P < 0.05$ corrected for small volume examined] in the right anterior fusiform locus identified by the face localizer.

Discussion

G.K. showed preserved detection of single stimuli in his left and right visual fields, but demonstrated profound left-sided extinction for bilateral visual stimuli, as a consequence of his circumscribed right inferior parietal lesion. Even with

fairly large stimuli, he reported seeing only the rightmost stimulus on virtually every trial with bilateral stimulation.

Past studies have shown with purely behavioural studies that some residual processing can still take place for extinguished visual stimuli (for review, see Driver, 1996), despite the pathological absence of awareness. However, no study to date had succeeded in identifying the neural basis of this residual processing conclusively. Here we identified the neural correlates of processing for extinguished stimuli in the parietal patient G.K. by comparing fMRI responses on trials where he showed extinction for bilateral stimulation (reporting the presence of only the right unilateral stimulus), versus those for right unilateral stimulation alone (where the same report was made). Differential fMRI activity was found in right hemisphere visual cortex, contralateral to the extinguished stimulus (Table 1). The strongest and most reliable activations were in right striate and early extrastriate cortex (Fig. 2).

The differential activation in striate cortex was seen midway along the calcarine sulcus (Fig. 2). As the foveal representation of the visual field is located at the occipital pole in primary visual cortex, the location of this right striate activation is in keeping with the eccentric position of the extinguished stimulus in the left visual field. Moreover, when left visual field stimuli were shown in isolation, for which G.K. did report awareness, then the same early visual areas (striate and extrastriate) were again differentially activated in the right hemisphere (Table 1 and Fig. 2). Indeed, the changes in BOLD signal for these areas showed a similar

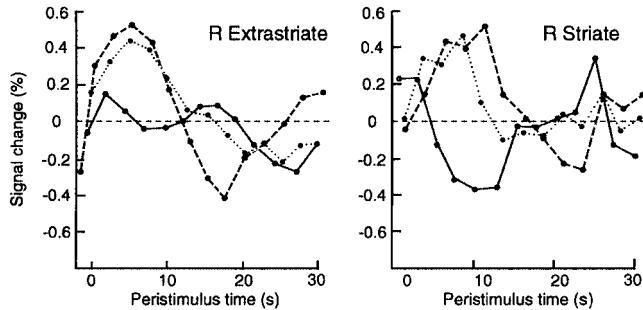


Fig. 3 Time-course of event-related activity in early visual cortex shown for illustrative purposes. The left graph plots the change in BOLD contrast (departure from the global mean), as a function of peristimulus time, for the right-hemisphere extrastriate cortical area shown in the lower row of Fig. 2. Activity is taken from the voxel of peak activation for the comparison of bilateral trials (showing extinction) minus unilateral right trials, weighted by the activity surrounding it with a Gaussian kernel of 6 mm full-width half-maximum. Separate line styles plot activity for one type of extinction trial (dashed: left house plus right face) versus the corresponding unilateral trials, on which just a left unilateral house was presented (dotted) or a right unilateral face (solid). This right-hemisphere area shows activity time-locked to the visual stimulus that is similar for trials where extinction of a left house occurred, versus trials where just a unilateral left house was presented. There is little differential activity when a right-sided face is presented. The right graph shows a similar peristimulus time plot of mean cortical activity for the right striate cortex area shown in the upper row of Fig. 2. Again, activity is taken from the voxel of peak activation (weighted by its surround) for the comparison of bilateral trials with extinction, minus unilateral right trials. Separate line-styles plot activity for one type of extinction trial (dashed: now a left face plus right house) versus the corresponding unilateral trials, on which just a left unilateral face was presented (dotted) or a right unilateral house (solid). Note again that this area also increases its activity following a left visual field stimulus, whether unilateral or extinguished, with no such increase for a right visual stimulus (if anything, some tendency for a decrease is apparent).

profile on both extinction and unilateral left trials, while little activity was evoked by right unilateral trials (see Fig. 3). Thus, the increase in BOLD contrast for these areas did not distinguish between unilateral left and extinguished trials. Taken together, these findings suggest that the same neural machinery was activated in early visual areas of the right hemisphere by a left visual field stimulus, whether seen or extinguished.

Our findings thus show that early contralateral visual areas, including primary visual cortex, can still be activated in the right hemisphere by an extinguished stimulus of which G.K. was unaware. This provides the first direct confirmation of previous theoretical claims (e.g. Driver, 1996; Mattingley *et al.*, 1997; Driver and Mattingley, 1998) that initial stages of visual processing may still proceed within the damaged hemisphere of parietal extinction patients. The clear activation of striate and extrastriate cortex by an extinguished stimulus provides a possible neural basis for some of the residual unconscious processing shown in previous behavioural

studies of extinction patients (e.g. Driver, 1996; Marzi, 1996; Mattingley *et al.*, 1997).

The activation of primary visual cortex in G.K. was strikingly similar for contralesional stimuli which escaped his awareness (i.e. extinguished stimuli on bilateral trials), compared with contralesional stimuli which he perceived (i.e. on left unilateral trials; see Figs 2 and 3). This might seem to support recent theoretical suggestions that people are not directly aware of activity in primary visual cortex (Crick and Koch, 1995), but some caution is appropriate on this issue. Our results clearly demonstrate that striate cortex can be activated without awareness in G.K. Moreover, as measured by fMRI, this striate activation appeared very similar to that for a consciously seen (unilateral) left stimulus. Nonetheless, it remains possible that there was some difference between conscious versus unconscious striate activity, that was not revealed by the fMRI experiment.

The activated cluster in right striate cortex for extinguished left stimuli appeared somewhat smaller in spatial extent than that for seen unilateral left stimuli (see Fig. 2). However, direct statistical comparison of these activations revealed no systematic difference; i.e. no voxels in this striate region were found which showed a reliably higher response for seen unilateral left stimuli than for extinguished left stimuli. A further possibility is that temporal rather than spatial details of the striate and extrastriate activations may have differed for conscious versus unconscious perception. There have been several recent suggestions that visual awareness may depend closely upon synchrony in neural firing (von der Malsburg, 1981; Engel *et al.*, 1991). fMRI is relatively insensitive to the fine-grained time-course of neural activity (even when used in an event-related design, as here), compared with other measures such as ERPs at the scalp. Only ERP measures depend on the synchrony of firing across many neurons, at the millisecond scale.

Marzi and colleagues recently conducted an ERP study of visual extinction in a different patient, using faint peripheral lights (Marzi *et al.*, 2000), rather than the large and meaningful objects (faces or houses) used here. They compared ERPs for bilateral stimulation trials on which extinction either did or did not occur. In the damaged (right) hemisphere, early P1 and N1 components of the visual evoked response were present on bilateral trials that were perceived correctly, but were absent or reduced for extinguished trials.

These ERP results suggest that the loss of awareness in extinction can affect early stages of vision, apparently in contrast to the preserved striate and extrastriate activation found in our own fMRI study. The apparent difference in outcome could reflect differences between the patients studied or the stimuli used. Of more theoretical interest, it might instead reflect fundamental differences in the sensitivity of fMRI and ERP measures to neural synchrony at fine timescales, as described above. Thus, striate and extrastriate areas may still activate (as shown by our fMRI data) for extinguished stimuli, yet with less synchrony in neural firing than for consciously perceived stimuli, which might resolve

the apparent discrepancy with the findings of Marzi and colleagues (Marzi *et al.*, 2000). Determining this will require both fMRI and ERP measures to be implemented for the same stimuli, in the same extinction patients. We and our collaborators are now pursuing this, as are other groups (e.g. Sagiv *et al.*, 2000; Vuilleumier *et al.*, 2000).

A further possibility is that instead of depending upon activation or synchrony within single areas, visual awareness may depend on the interaction or covariation between visual cortex and areas of parietal or frontal cortex (Crick and Koch, 1995; Lumer and Rees, 1999). The potential importance of interactions between occipital cortex and the parietal lobe in particular (Driver and Mattingley, 1998) is certainly supported by our findings in G.K., who showed a loss in visual awareness following parietal injury, despite structurally intact striate and extrastriate cortex that can evidently still be activated by contralateral stimuli, as our fMRI data show.

Our comparison of face and house stimuli was intended to reveal any category-specific processing that may still take place for extinguished stimuli in G.K., along the ventral object-recognition pathway of the visual system. Preserved ventral processing in parietal extinction has been suggested previously (Berti and Rizzolatti, 1992; Baylis *et al.*, 1993; McGlinchey-Berroth *et al.*, 1993; Driver, 1996; Driver and Mattingley, 1998) based on purely behavioural demonstrations of influences from extinguished stimuli (e.g. priming or interference effects) that depended upon their category or identity. We indeed found some evidence for category-specific responses to faces (versus houses) when extinguished in G.K., within the fusiform gyrus, but only at low statistical threshold.

Within the region of interest predefined by the entirely independent, blocked face localizer (specifically, within the right fusiform gyrus), some differential response was apparent to an extinguished face versus extinguished house. Given the low statistical significance of this particular result, in contrast to the more robust striate and extrastriate activations, we will not place much emphasis upon it. The relative weakness of this activation may have been due to the peripheral and brief stimuli used, in contrast to the long-duration foveal stimulation used in the face localizer (and also in most previous studies of category-specific activations in the ventral pathway; e.g Haxby *et al.*, 1991; Kanwisher *et al.*, 1997; Ishai *et al.*, 1999). Consistent with this, activation was still relatively weak within the fusiform gyrus even for consciously seen faces versus houses in our extinction study, on the unilateral trials. Nevertheless, the low-threshold face-selective response we observed in the right fusiform gyrus of G.K. for extinguished objects may still provide a neural basis for the residual processing of object-category found for extinguished stimuli in past behavioural studies (e.g. Berti and Rizzolatti, 1992; McGlinchey-Berroth *et al.*, 1993). As discussed at length by Farah (Farah, 1994), many of the unconscious priming and interference effects from extinguished stimuli in previous behavioural work could, in principle, be produced by weak activations along the ventral

pathway, like those we observed directly for G.K. in the fusiform gyrus. Moreover, Zeki and ffytche specifically proposed that residual unconscious processing may depend on low-levels of activation (Zeki and ffytche, 1998).

Conclusion

Our event-related fMRI results show that, in a patient with left-sided extinction following circumscribed damage to the inferior parietal lobule of the right hemisphere, an extinguished left visual field stimulus can still activate visual cortex in the right hemisphere, including striate and early extrastriate areas. fMRI activity in these areas was time-locked to stimulation and similar to that produced by a single stimulus in the left visual field. This suggests that the initial cortical pathways involved in normal processing of a single, consciously seen stimulus can still be activated by an unseen, extinguished stimulus. Our results thus imply that activation of primary visual cortex (and early extrastriate cortex) by a visual stimulus is not sufficient to evoke awareness. It remains possible that the synchrony of neural firing in such areas and/or their interaction with other areas (such as the damaged inferior parietal lobule), normally plays a critical role in awareness.

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