Neural response to emotional faces with and without awareness: event-related fMRI in a parietal patient with visual extinction and spatial neglect

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Abstract

This study examined whether differential neural responses are evoked by emotional stimuli with and without conscious perception, in a patient with visual neglect and extinction. Stimuli were briefly shown in either right, left, or both fields during event-related fMRI. On bilateral trials, either a fearful or neutral left face appeared with a right house, and it could either be extinguished from awareness or perceived. Seen faces in left visual field (L VF) activated primary visual cortex in the damaged right hemisphere and bilateral fusiform gyri. Extinguished left faces increased activity in striate and extrastriate cortex, compared with right houses only. Critically, fearful faces activated the left amygdala and extrastriate cortex both when seen and when extinguished; as well as bilateral orbitofrontal and intact right superior parietal areas. Comparison of perceived versus extinguished faces revealed no difference in amygdala for fearful faces. Conscious perception increased activity in fusiform, parietal and prefrontal areas of the left-hemisphere, irrespective of emotional expression; while a differential emotional response to fearful faces occurring specifically with awareness was found in bilateral parietal, temporal, and frontal areas. These results demonstrate that amygdala and orbitofrontal cortex can be activated by emotional stimuli even without awareness after parietal damage; and that substantial unconscious residual processing can occur within spared brain areas well beyond visual cortex, despite neglect and extinction.

Keywords: Visual neglect; Visual extinction; Emotion; Faces; Amygdala; Awareness

1. Introduction

Fast detection of potential threats is important for many organisms. It has been suggested that the amygdala may constitute a dedicated system for processing danger and emotionally-relevant events, especially when these occur outside attention or awareness [4,30,31]. Studies of fear-conditioning in animals suggest that the amygdala may receive direct thalamic inputs bypassing striate and extrastriate visual cortex [4,31]. Functional imaging studies in humans reported amygdala activation by emotional stimuli, such as fearful or fear-conditioned faces, even when masked and hence not detected by healthy subjects [36,37,51]. Similarly, the amygdala can still be activated by fearful faces when these are task-irrelevant and outside the focus of attention [46]. Moreover, behavioural findings indicate that normal observers may exhibit automatic responses (such as discriminative skin conductance changes) to emotional stimuli that are neither overtly attended nor consciously detected (e.g. [17]).

In the present study, we used event-related fMRI in a patient with hemispatial neglect and visual extinction, to investigate the neural responses evoked by emotional faces with and without conscious perception. Neglect often follows right inferior parietal damage, and is characterised by impaired attention and lack of awareness for stimuli on the contralesional (left) side of space [24]. Such patients may have intact visual fields but show perceptual extinction, i.e. they may fail to detect a stimulus in the contralesional field when it is presented with a concurrent stimulus in the ipsilesional field, although the same contralesional stimulus can be detected when presented alone [7,13,42]. In these patients, visual pathways into occipital and temporal cortex may be anatomically spared,
including the amygdala. Behavioural findings and recent functional imaging studies suggest that these intact visual pathways can still sustain some residual “implicit” processing of extinguished stimuli, despite the patients’ unawareness [8,43,47]. Likewise, emotional significance of stimuli may be detected despite contralesional inattention on bilateral simultaneous events. Extinction can be less for faces with an emotional than neutral expression [48], or for threat-related stimuli, such as spiders than neutral stimuli, such as flowers [49]. A plausible neural substrate for this preserved processing of contralesional emotional stimuli might involve the amygdala, possibly interacting with intact visual areas to prioritise awareness for salient stimuli [4,30,35].

Our study examined the neural correlates of emotional face processing, associated with either awareness or unawareness of the faces, in a patient who had a focal right-parietal lesion with intact visual fields and reliable left visual extinction on bilateral simultaneous stimulation (BSS). Photographs of faces with neutral or fearful expressions were presented either alone in the right visual field (RVF) or left visual field (LVF), or in the LVF together with a concurrent photograph of a house in the RVF (BSS). The critical events were the latter BSS trials, where our patient extinguished a substantial proportion of left-side faces. The major questions were whether extinguished fearful faces would still elicit emotional responses in amygdala and other limbic structures; and whether these responses would differ as a function of awareness versus extinction of the faces. Our main analysis could therefore employ a 2 × 2 factorial design for the critical BSS trials, testing for the main effects of emotion (neutral or fearful face in LVF) irrespective of awareness; as well as for any interaction of such emotional effects with awareness of the faces (versus extinction). In addition, we could also contrast BSS trials with an extinguished LVF face to unilateral trials with a RVF house alone (same conscious percept reported), allowing us to examine any implicit effects due to extinguished stimuli [43,47].

2. Materials and methods

2.1. Patient

GK is a 69-year-old man, who suffered a right-hemisphere infarction 2 years prior to the current study, centred on posterior inferior parietal region and underlying white matter (Fig. 1). On neurological examination, he still showed a mild loss of dexterity and position-sense in the left hand, reliable left extinction on bilateral simultaneous visual (and tactile) stimulation, and intact visual fields on both sides. He scored 87 on the standardised behavioural inattention test (<cut-off 129) and still showed moderate left spatial neglect in standard clinical tests, such as Mesulam cancellation task (25 left-side omissions per 60 targets) at the time of investigation. Additional behavioural [25] and imaging [43] data were previously reported.
appearing briefly (600 ms) on either side (back-projected on a mirror mounted on the head-coil, and Ekman and Friesen [16]) and 10 houses were used (Fig. 2), within the same day (9 min each). The task was similar to unilateral L VF trials. Discrimination based on outer contours. Response keys were then transformed to a normal distribution (SPM Z). Activities were selected only if surviving a threshold of P = 0.001 uncorrected at the voxel level, with a significance of P < 0.05 at the cluster level. A small volume correction (SVC) using an 8 mm sphere was applied to P-values for the amygdala where indicated, in keeping with a priori hypothesis of amygdala involvement in the processing of fearful expressions [52]. For descriptive purposes, we also report additional foci passing an uncorrected threshold of P < 0.001 at the voxel level when not significant at the cluster level if these were consistent with a priori predictions.

2.2. Behavioural task outside the scanner

GK was trained on our extinction-task, a few days before scanning, using different stimuli to those subsequently shown in the scanner. A further training session was given in the scanner just before the actual fMRI session, again using different stimuli. During these sessions, photographs of faces and houses were presented either unilaterally on the left- or right-side, or bilaterally on both sides, with the probabilities of bilateral versus unilateral, left versus right, and face versus house stimuli all equally balanced. Bilateral trials included a face on one side and a house on the other side, with faces equally often in the L VF or RVF. All trial types were intermingled in random order. The patient reported by key-presses via his ipsilesional hand whether he saw a face (thumb response), a house (index), or both stimulus types (middle finger). To ensure central fixation during the task, each trial began with a fixation point at the centre of the screen which turned either green or red 750 ms before stimulus onset, instructing the patient either to respond normally (green “go” fixation; 2/3 trials) or to withhold from responding (red “no-go” fixation; 1/3 trials). On 15% of trials (catch), a fixation point was not followed by any stimulus. An error message and a loud warning sound followed incorrect key-presses. During these training sessions, GK failed to detect a face or house in the L VF on 40–100% of bilateral displays, depending on exposure duration (100–1000 ms in different blocks). His performance during the final training-blocks, inside the scanner, was used to determine stimulus duration for the subsequent scanning sessions (600 ms), with the aim of obtaining ~50% of extinction on critical BSS trials, yet with reliable detection on unilateral L VF trials.

2.3. Experimental task inside the scanner

Three successive fMRI scanning sessions were performed within the same day (9 min each). The task was similar to the previous training, except for a different proportion of trial types and a different set of stimuli. Ten faces (from Ekman and Friesen [16]) and 10 houses were used (Fig. 2), back-projected on a mirror mounted on the head-coil, and appearing briefly (600 ms) on either side (~8° away from fixation, ~2° of visual angle each). All faces and houses were shown within the same black oval frame to avoid discrimination based on outer contours. Response keys were mounted on a custom-made glove attached to the unseen right hand. The critical events were BSS with a L VF face and a RVF house, where the face had either a neutral or fearful expression (24 trials for each of these conditions per session). Based on training data, we expected that the patient would extinguish the L VF faces (~50%) of these trials. No BSS trials with a RVF face and a L VF house occurred during actual scanning, in order to minimise the number of trial types, and so optimise our statistical power for the critical experimental comparisons. There were unilateral events with a fearful or neutral face in L VF or RVF (six trials each per session), and unilateral events with a house in L VF or RVF (6 and 12 trials per session, respectively). As in training, trials began with a green (go) or red (no-go) fixation point, but the latter now occurred only on some unilateral trials with a left-side house or right-side face (9% of total trial types). All trial types were similarly randomised and distributed in the three scanning sessions, with a mean interval of 5.1 s (randomly jittered between 4.5 and 13 s).

2.4. fMRI imaging

MRI data were acquired on a 2T Siemens VISION system with a head volume coil. Functional images were acquired with a gradient echo-planar T2* sequence using BOLD (blood oxygenation level dependency) contrast. A total of 460 functional images were taken during three scanning sessions (32 contiguous axial slices, 3 mm thickness), in addition to eight dummy images at the beginning of each session that were subsequently discarded, to allow for T1 equilibration effects. TR was 2.93 s and average inter-stimulus time was 5.1 s. A structural MRI scan was also acquired using a T1-weighted sequence to obtain anatomical images of the patient’s brain and lesion.

The fMRI data were analysed using the general linear model for event-related designs in SPM99 (http://fil.ion.ucl.ac.uk/spm) implemented in MATLAB. Scans were re-aligned, normalised, time-corrected, and spatially smoothed by an 8 mm FWHM gaussian kernel [5,19]. Low-pass and high-pass frequency filters were applied to the time series. Individual events were modelled by a standard synthetic haemodynamic response function and its temporal derivative. Bilateral trials in which the left face was perceived versus extinguished (as determined by the patient’s responses during scanning) were modelled separately, as were trials with unilateral L VF faces. Movement parameters derived from the realignment correction (for all six possible directions) were also entered into the design matrix as covariates of no interest. Analysis generated statistical parametric maps of the t-statistic (SPM (t)), resulting from linear contrasts between different event conditions, which were then transformed to a normal distribution (SPM (Z)). Activations were selected only if surviving a threshold of P = 0.001 uncorrected at the voxel level, with a significance of P < 0.05 at the cluster level. A small volume correction (SVC) using an 8 mm sphere was applied to P-values for the amygdala where indicated, in keeping with a priori hypothesis of amygdala involvement in the processing of fearful expressions [52]. For descriptive purposes, we also report additional foci passing an uncorrected threshold of P < 0.001 at the voxel level when not significant at the cluster level if these were consistent with a priori predictions.
Fig. 2. Example stimuli. Critical trials were BSS with a face in the LVF and a house in the RVF, where the face was either consciously perceived or extinguished by the patient. Faces had either a fearful or neutral expression (half of trials each). A central fixation point instructed the patient either to respond by a key-press (indicating whether just a house was seen, just a face, or both stimulus types) if it was green (90% of trials during scanning) or to withhold from responding if it was red (10% of trials during scanning), thus ensuring accurate central fixation. Neural effects produced by extinguished (fearful or neutral) faces were examined by contrasting the critical BSS trials against unilateral trials with a right house alone. Neural effects produced by consciously seen faces were examined by comparing BSS trials with detected versus extinguished faces. The critical BSS trials allowed a factorial analysis testing the effect of emotion (fearful or neutral) and perception (extinguished or detected) for LVF faces separately, as well as any interaction between these two factors.

3. Results

3.1. Behavioural performance during fMRI

Across the three scanning sessions, the patient correctly reported 93% of unilateral faces and houses in the RVF. He missed only 37% of unilateral faces in the LVF, with no difference between faces with fearful and neutral expression, and no misidentification errors between faces and houses. On the critical bilateral trials, he missed 68% of left-side neutral faces and 63% of left-side fearful faces. This demonstrates a significant extinction pattern, with perception of LVF stimuli relatively preserved for a single stimulus, but compromised by a competing RVF stimulus ($\chi^2(1) = 21.6, P < 0.001$). Fearful faces underwent less extinction than neutral faces on the first and second sessions (55% versus 75% missed and 88% versus 100%, respectively, $\chi^2(1) = 4.04, P = 0.044$), but not on the third (46% versus 33%). The patient correctly withheld response on all but one “no-go” trial.

3.2. Functional imaging

3.2.1. Conscious perception

We first examined neural responses evoked by visual stimuli consciously seen by the patient. Areas specifically activated by LVF stimuli were determined by comparing all unilateral left versus right trials, when the patient correctly reported the stimuli, regardless of category (i.e. faces or houses). Activation was found in striate occipital cortex and posterior lingual gyrus of the right (damaged) hemisphere, together with activations in left inferior parietal cortex and insula (Table 1). Unilateral trials were also used to determine
areas responding more to faces than to houses, regardless of side (LVP or RVP) and expression. This revealed activations in right fusiform gyrus and bilateral inferior temporal cortex (Table 1 and Fig. 3A). These results are in accordance with previous findings in normal subjects (e.g. [23,26]) and in this patient [43].

The effect of emotional expression, when faces were consciously seen, was assessed by a conjunction analysis [41] looking at areas commonly activated by fearful more than neutral faces across different conditions, i.e. both on unilateral trials with a RVP face and on bilateral trials with a perceived LVP face. (Unilateral LVP faces were not included in this conjunction because of an insufficient number of such events for each expression.) Increased activity due to fearful facial expression was observed in left amygdala and left fusiform gyrus (Fig. 3B), as well as in the left retrosplenial cortex, left orbitofrontal cortex, and right anterior middle frontal gyrus (Table 1). Right amygdala activation was also present but did not survive correction for multiple comparisons (Table 1). All these areas have previously been implicated in emotional face processing for normal subjects (e.g. [10,35,37,51]).

3.2.2. Unconscious perception in bilateral trials

We next examined the neural response evoked by extinguished faces (regardless of expression). Bilateral trials with an unseen face in the LVP and a house in the RVP (BSS extinguished) were compared to unilateral trials with a RVP house alone (i.e. events associated with same awareness and response, but different contralesional stimuli). This revealed significant activations in bilateral occipital areas, including peaks in right primary visual cortex and bilateral cuneus (Table 2). These results confirm other fMRI data on extinction [43,47] showing activation of right posterior visual cortex by unseen LVP stimuli.1

Table 1

Activations produced by consciously seen stimuli

<table>
<thead>
<tr>
<th>Side</th>
<th>Brain areas</th>
<th>Coordinates</th>
<th>Z-score</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>LVP &gt; RVP (regardless of stimulus type)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>R</td>
<td>Lingual gyrus</td>
<td>32</td>
<td>−78</td>
<td>−16</td>
</tr>
<tr>
<td>L</td>
<td>Posterior insula</td>
<td>−38</td>
<td>−18</td>
<td>20</td>
</tr>
<tr>
<td>R</td>
<td>Striate cortex (anterior)</td>
<td>10</td>
<td>−96</td>
<td>−10</td>
</tr>
<tr>
<td>R</td>
<td>Striate cortex (anterior)</td>
<td>8</td>
<td>−74</td>
<td>2</td>
</tr>
<tr>
<td>L</td>
<td>Supramarginal gyrus</td>
<td>−56</td>
<td>−38</td>
<td>22</td>
</tr>
<tr>
<td>L</td>
<td>Supramarginal gyrus</td>
<td>−50</td>
<td>−38</td>
<td>16</td>
</tr>
<tr>
<td>Faces &gt; houses (regardless of field)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>L</td>
<td>Lingual gyrus</td>
<td>−18</td>
<td>−82</td>
<td>−6</td>
</tr>
<tr>
<td>L</td>
<td>Inferior occipital gyrus</td>
<td>−12</td>
<td>−92</td>
<td>−20</td>
</tr>
<tr>
<td>R</td>
<td>Fusiform gyrus</td>
<td>30</td>
<td>−60</td>
<td>−20</td>
</tr>
<tr>
<td>Fearful &gt; neutral faces</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>L</td>
<td>Fusiform gyrus</td>
<td>−32</td>
<td>−70</td>
<td>−14</td>
</tr>
<tr>
<td>L</td>
<td>Retrosplenial cortex</td>
<td>−18</td>
<td>−58</td>
<td>26</td>
</tr>
<tr>
<td>L</td>
<td>Amygdala</td>
<td>−30</td>
<td>6</td>
<td>−34</td>
</tr>
<tr>
<td>R</td>
<td>Amygdala</td>
<td>24</td>
<td>−6</td>
<td>−34</td>
</tr>
<tr>
<td>R</td>
<td>Middle frontal gyrus</td>
<td>42</td>
<td>56</td>
<td>−4</td>
</tr>
<tr>
<td>L</td>
<td>Lateral orbitofrontal</td>
<td>−30</td>
<td>30</td>
<td>−24</td>
</tr>
<tr>
<td>L</td>
<td>Cerebellum</td>
<td>−28</td>
<td>−42</td>
<td>−40</td>
</tr>
</tbody>
</table>

All activations survived a threshold of P < 0.05 at the cluster level, except *P < 0.05 corrected for volume of interest. **P < 0.001 uncorrected.

Coordinates refer to normalised Talairach & Tournoux stereotactic space, but anatomical areas correspond to the patient’s own brain as defined from his MRI scan.

1 We also examined areas with increased activity for the opposite contrast of extinguished versus perceived stimuli in LVP (regardless of category). This revealed selective activation of cuneus (x = −8, y = −66, z = −26, Z = 4.58) and peristriate cortex (x = −14, y = −58, z = 14, Z = 3.84) in left medial occipital lobe. Such increases in the intact hemisphere on extinction trials might reflect the neural effects of a competition between bilateral perceived stimuli across hemifields [18].

3.2.3. Conscious and unconscious perception of emotional faces in bilateral trials

A major concern in our study concerned the neural response to emotional stimuli when extinguished from awareness. The critical BSS trials constituted a 2 × 2 factorial analysis allowing us to determine main effects of emotion (fearful versus neutral expression) and awareness (consciously seen versus extinguished faces) separately, as well as any significant modulation of emotional responses as a function of awareness (interaction term).

The main effect of fear (BSS with seen + extinguished fearful faces > BSS with seen + extinguished neutral faces) identified brain regions responding to emotional expressions irrespective of whether the face was consciously seen or not. In keeping with the findings above, such increases were
Fig. 3. Peaks of activation shown superimposed on the structural MRI brain scan of the patient. (A) Activity specifically evoked by consciously seen faces, as opposed to seen houses, was observed in the right fusiform cortex \((x = 30, y = -60, z = -20)\), irrespective of emotional expression and field of presentation. (B) Activity specifically evoked by faces with a fearful expression, as opposed to neutral expression, was observed in the left amygdala, with two peaks merging anteriorly \((x = -30, y = 6, z = -34\) and \(x = -20, y = 0, z = -36\), encircled in red), as well as in the left fusiform cortex \((x = -32, y = -70, z = -46)\) and left lateral orbitofrontal cortex \((x = -30, y = 30, z = -24\), not shown here), irrespective of field of presentation. Activity in the fusiform cortex, but not in left amygdala and orbitofrontal cortex, was modulated by awareness of the faces, as opposed to extinction (see Fig. 4).

<table>
<thead>
<tr>
<th>Side</th>
<th>Brain area</th>
<th>Coordinates</th>
<th>Z-score</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>L</td>
<td>Posterior lingual gyrus</td>
<td>(-8)</td>
<td>(-74)</td>
<td>2</td>
</tr>
<tr>
<td>L</td>
<td>Pulvinar</td>
<td>(-12)</td>
<td>(-28)</td>
<td>4</td>
</tr>
<tr>
<td>L</td>
<td>Fusiform gyrus</td>
<td>(-18)</td>
<td>(-50)</td>
<td>(-22)</td>
</tr>
<tr>
<td>L</td>
<td>Cuneus</td>
<td>(-8)</td>
<td>(-70)</td>
<td>32</td>
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<tr>
<td>R</td>
<td>Cuneus</td>
<td>10</td>
<td>(-92)</td>
<td>18</td>
</tr>
<tr>
<td>R</td>
<td>Striate cortex</td>
<td>0</td>
<td>(-86)</td>
<td>2</td>
</tr>
<tr>
<td>L</td>
<td>Inferior temporal gyrus</td>
<td>(-46)</td>
<td>(-26)</td>
<td>(-22)</td>
</tr>
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</table>

Only extinguished fearful faces > RVF alone

<table>
<thead>
<tr>
<th>Side</th>
<th>Brain area</th>
<th>Coordinates</th>
<th>Z-score</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>L</td>
<td>Amygdala</td>
<td>(-26)</td>
<td>0</td>
<td>(-28)</td>
</tr>
<tr>
<td>R</td>
<td>Posterior lingual gyrus</td>
<td>10</td>
<td>(-76)</td>
<td>0</td>
</tr>
</tbody>
</table>

Only extinguished neutral faces > RVF alone

No additional foci.

All activations survived a threshold of \(P < 0.05\) at the cluster level, except \(^* P < 0.05\) corrected for volume of interest, \(^{**} P < 0.001\) uncorrected. Coordinates refer to normalised Talairach & Tournoux stereotactic space, but anatomical areas correspond to the patient’s own brain as defined from his MRI scan.
found in left amygdala (Table 3), together with left fusiform cortex, left orbitofrontal cortex, and right intraparietal sulcus (Table 3). All these regions responded to fearful more than neutral expressions regardless of awareness.

The main effect of awareness (BSS with seen fearful + seen neutral faces > BSS with extinguished fearful + extinguished neutral faces) tested for regions specifically activated by conscious perception of faces in the L VF (as opposed to extinction), irrespective of emotional expression, for physically equivalent displays. This revealed significant increases in several areas of the left-hemisphere (Table 3), including left fusiform, left parietal, and left frontal cortex.

Finally, the most direct test for determining the extent to which the response to fearful faces was modulated by awareness of the faces is to identify brain regions showing an interaction between emotion and awareness on BSS trials, responding more to fear when faces were perceived versus extinguished (IBSS with seen fearful faces > seen neutral faces)–[BSS with extinguished fearful faces = extinguished neutral faces)]. Significant increases were found in left fusiform gyrus, plus bilateral anterior parietal regions, right anterior temporal pole, and bilateral frontal cortex (Table 3 and Fig. 4). Notably, this interaction was not significant in the left amygdala even at a liberal statistical threshold (Z = 1.58, P = 0.057 uncorrected, P = 0.64 corrected).

### 3.2.4. Comparison of fearful and neutral faces in extinguished bilateral trials

An additional analysis to confirm emotional responses without conscious perception (e.g. in amygdala) examined BSS trials in which either fearful or neutral faces were extinguished in the L VF, compared with RVF houses alone. This showed that extinguished fearful faces produced significant activation of left amygdala (Z = 3.41, P < 0.05 corrected for small volume) in addition to activating other striate and extrastriate visual areas (Table 2). By contrast, unseen neutral faces in extinguished BSS versus unilateral RVF trials did not produce a reliable effect in the left amygdala (Z = 1.98, P = 0.024 uncorrected, P = 0.58 corrected).

Direct comparison of all extinguished faces revealed that unseen fearful as opposed to unseen neutral faces increased activity in several areas including bilateral lingual gyrus (x = 12, y = −76, z = −2, Z = 4.52; and x = 18, y = −60, z = −6, Z = 4.07), bilateral orbitofrontal cortex (x = 4, y = 50, z = −20, Z = 4.35; and x = −18, y = 32, z = −14, Z = 4.05), left pulvinar (x = 18, y = −32, z = 2, Z = 4.29), and right superior intraparietal sulcus (x = 36, y = −74, z = 44, Z = 4.40; all P < 0.001 uncorrected, P < 0.05 at the cluster level). This contrast did not reach significance in the amygdala (Z = 1.37, P = 0.086 uncorrected, P = 0.75 corrected), but the lack of a significant amygdala effect for this comparison can be
Fig. 4. Size of activation for activated brain areas shown in Fig. 3 (peak voxels weighted by smoothing of their surround), averaged across conditions and scanning sessions (arbitrary units). (A, B) Activity in both right and left fusiform cortex increased when faces were consciously perceived, as opposed to extinguished, irrespective of emotional expression. In addition, bilateral fusiform areas showed an enhanced response to fearful as compared to neutral expression, both when the faces were perceived or extinguished. (C) Activity in left amygdala increased in response to fearful faces both when consciously perceived and extinguished. The left amygdala also showed a weak response to neutral faces when these were extinguished, but no response to neutral faces when these were consciously seen (irrespective of field of presentation, in unilateral right or bilateral trials). (D) The lateral orbitofrontal cortex also responded to fearful faces during both conscious perception and extinction.

explained by a closer inspection of amygdala activity across conditions. As Fig. 4 shows, the left amygdala response to neutral faces was higher when the faces were extinguished than when consciously perceived. This unexpected increase in activity for neutral faces with extinction, versus conscious perception, was significant ($Z = 3.61, P < 0.05$ corrected for small volume).

4. Discussion

In this right-parietal patient with left neglect and extinction, consciously perceived faces with a fearful expression activated bilateral visual areas in fusiform gyri and adjacent temporo-occipital cortex, as well as the left amygdala and other emotion-related regions in mediofrontal and orbitofrontal cortex. This pattern is consistent with findings in neurologically intact subjects [10,23,26,35,37,46,51]. Our novel results demonstrate that several areas responded to the emotional significance of faces irrespective of awareness. In particular, the left amygdala was activated by fearful faces in the contralesional LVF both when seen and when extinguished. Moreover, we found no interaction between emotion and awareness in the amygdala. In our factorial analysis, the left amygdala exhibited a main effect of fearful expression without any additional effect due to awareness of
the faces (see Table 3), suggesting that its response to fear was not significantly modulated as a function of conscious perception versus extinction.

Other areas also responded to fearful more than neutral faces regardless of awareness, including left fusiform, lateral orbitofrontal, and right intraparietal cortex (superior to the lesion). Our novel findings for orbitofrontal cortex appear consistent with a recent report of unconscious responses to subliminal stimuli in orbitofrontal cortex, as revealed by intracerebral event-related potentials in human subjects [9]. By contrast, left fusiform cortex was more activated by consciously perceived versus extinguished faces, irrespective of expression. This accords with previous evidence that fusiform activity correlates with awareness of faces in normal subjects [20,45].

Our results provide a possible neural substrate for recent behavioural findings in patients with spatial neglect and extinction [48,49] suggesting that emotional properties of contralesional stimuli can be extracted despite pathological inattention and unawareness. Our findings show that processing of extinguished stimuli can proceed well beyond early visual pathways. This extends previous neuropsychological observations of residual processing based on visual grouping [13] or object recognition mechanisms [8], thought to depend on occipito-temporal areas. It also extends recent fMRI data showing activation of primary visual cortex and posterior temporal regions by extinguished stimuli [14,43,47]. Here, extinguished fearful faces activated not only extrastriate visual cortex, but also left amygdala, in anterior and medial regions of the temporal lobe, as well as orbitofrontal cortex and superior parietal cortex, all structurally spared by the lesion in GK. This suggests that extinguished emotional stimuli can receive substantial processing in distributed brain areas, quite distant from early sensory cortex, yet still not reach awareness.

4.1. Emotional responses without awareness

These results support proposals that the amygdala can process fear-related information with a large degree of automaticity, e.g. without conscious perception or selective attention [4,31]. Other PET and fMRI studies in normal subjects demonstrated amygdala responses to fear-conditioned stimuli [11,29] and fearful faces [10,35,37,51], even when explicit perception of the faces was suppressed in healthy subjects by masking [36,51] or inattention [46], or when faces were presented in the scotoma of a patient with blindsight [34]. In our patient, the left amygdala was still activated when he extinguished fearful faces in LVF and reported only the presence of a RVF house, indicating that the amygdala may detect emotionally-relevant stimuli despite attention being engaged by another competing stimulus at a separate location. Taken together, these results suggest that emotional inputs to the amygdala may be at least partly independent of processing in occipital and fusiform cortex associated with visual awareness.

Previous anatomical and imaging data have pointed to a subcortical route (via superior colliculus and pulvinar) for rapid and unconscious inputs to the amygdala, bypassing primary visual cortex [31,34]. In GK, extinguished faces increased activity of left pulvinar, more when faces were fearful than neutral. However, extinguished faces in the LVF (as compared to RVF houses alone) also activated right primary visual cortex and bilateral extrastriate areas (see Table 2). Inputs from extinguished stimuli engaging either the pulvinar or visual occipital cortex might still project to fusiform areas [12] at a level below threshold for conscious perception of a face, but sufficient to trigger an amygdala response.

Face-selective fusiform areas showed an enhanced response to fearful as compared to neutral expression, both when the faces were perceived or extinguished (see Fig. 3). This was additive to an increase associated with awareness versus extinction. Such emotional enhancement could reflect feedback influences from amygdala on fusiform cortex, independent of awareness and attention [1,35,46]. This would converge with recent results from single-cell recording in temporal cortex of the monkey [44] and functional imaging in healthy humans [35,46].

The lateral orbitofrontal cortex was also activated by extinguished fearful faces, and receives direct inputs from the amygdala [1]. Orbitofrontal cortex has been implicated in emotional processing across a variety of conditions (e.g. [39,46]). Moreover, activity in both orbitofrontal and parietal areas has recently been associated with faster orienting of spatial attention towards emotional stimuli [3], as found behaviourally in healthy subjects [33] and in some parietal patients despite hemispatial neglect [48,49]. An enhanced processing of emotional stimuli in fusiform and orbitofrontal areas might underlie the greater salience of such stimuli for perceptual awareness. Here, however, GK detected fearful better than neutral faces only during the first and second scan sessions, not the third. It is possible that emotional effects on attention and awareness are liable to habituation [10,11], especially after repeated exposure to the same stimuli, as here.

4.2. Differences in neural responses with and without awareness

An unexpected finding was that neutral faces activated the amygdala more when extinguished than when consciously perceived (see Fig. 4). We speculate that a neutral face represents more potential threat when outside the current focus of attention, consistent with a more general function for the amygdala processing of salient stimuli with social and emotional meaning, beyond just fear recognition and conditioning [32,50]. Increased amygdala activity has also been found for neutral faces of strangers versus familiar people [15], social out-group versus in-group [22,40], or direct eye-contact versus averted gaze [21,27]. Moreover, several studies found that masked stimuli (including angry faces and aversive pictures) can elicit stronger emotional behavioural reactions and greater amygdala activation than the same stimuli when
unmasked [2,28,33]. This may accord with the view that while crude emotional processing can take place rapidly and unconsciously, the engagement of conscious cognitive processes can modify or suppress these evaluations [38].

Finally, the present study corroborates and extends other recent fMRI data on visual extinction after parietal damage. These results demonstrate that contralesional stimuli can activate intact visual cortex in the damaged hemisphere, despite unawareness [43,47]. On the other hand, the same contralesional stimuli can produce greater activation in several areas of the left-hemisphere when consciously perceived, including fusiform, posterior parietal, and inferior frontal cortex. Differential eye-position cannot be entirely ruled out and might in principle contribute, though note that a colour monitoring task was performed at central fixation to minimise this. Moreover, even if unintended rightward saccades were more frequent on extinguished trials, this would not undermine our most critical findings of a differential effect for extinguished LVF emotional stimuli. The pattern of left-hemisphere activation associated with conscious versus unconscious perception of contralesional faces was remarkably similar in this study and a previous investigation [47], with a different patient and different stimuli. Although some of these left-hemisphere activations (e.g. inferior frontal cortex) could in principle reflect covert verbal processes (not strictly required by the task), rather than visual awareness per se, this seems unlikely to explain all these activations, given the specific anatomical loci observed. Moreover, it is increasingly thought that visual awareness may reflect the availability of information to a diffuse network (including but not restricted to availability for verbal report) (e.g. [6]), rather than merely activation within visual cortex as traditionally conceived.

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