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Asymmetrical Activation in the Human Brain during Processing of Fearful Faces

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Summary

Traditional split-field studies and patient research indicate a privileged role for the right hemisphere in emotional processing [1–7], but there has been little direct fMRI evidence for this, despite many studies on emotional-face processing [8–10] (see Supplemental Background). With fMRI, we addressed differential hemispheric processing of fearful versus neutral faces by presenting subjects with faces bilaterally [11–13] and orthogonally manipulating whether each hemifield showed a fearful or neutral expression prior to presentation of a checkerboard target. Target discrimination in the left visual field was more accurate after a fearful face was presented there. Event-related fMRI showed right-lateralized brain activations for fearful minus neutral left-hemifield faces in right visual areas, as well as more activity in the right than in the left amygdala. These activations occurred regardless of the type of right-hemifield face shown concurrently, concordant with the behavioral effect. No analogous behavioral or fMRI effects were observed for fearful faces in the right visual field (left hemisphere). The amygdala showed enhanced functional coupling with right-middle and anterior-fusiform areas in the context of a left-hemifield fearful face. These data provide behavioral and fMRI evidence for right-lateralized emotional processing during bilateral stimulation involving enhanced coupling of the amygdala and right-hemispheric extrastriate cortex.

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Results

We presented bilateral face displays to create a situation that may maximize laterality effects in accordance with studies [11–13] suggesting that behavioral visual-field effects can be more apparent during bilateral stimulation of both fields than during stimulation of one field, as also reported for emotional stimuli [14–15]. The faces either had the same (fearful or neutral) facial expression on both sides ("symmetrical" type) or had one side fearful and the other neutral ("asymmetrical"). The faces themselves were irrelevant to the task, which comprised discrimination of a deviant square (when present) in one of two checkerboards presented shortly after the faces were presented (Figure 1). Checkerboards were used as target stimuli to evaluate the effect of emotional stimuli on visual hemifield while keeping the faces themselves task irrelevant.

In a behavioral study (see Behavioral Results), we found enhanced checkerboard performance specifically in the left visual field (LVF) after the presentation of a LVF fearful face, regardless of the type of face shown concurrently in the right visual field (RVF). This suggests that a LVF emotional face can modulate some aspect of visual processing on that side. We examined neural substrates in a functional magnetic resonance imaging (fMRI) study that focused on visually responsive and face-responsive areas. Some previous studies reported enhanced activation of extrastriate cortex with nonlateralized faces [16–18]. Here, we sought to test for possible laterality effects and also for any role of modulatory interactions with the amygdala [19–21], a region known to play a key role in aspects of emotional processing [22–24] and to be activated by fearful faces [16, 25]. Some studies suggested a prominent role for the right amygdala in fear processing [26–27].

We used two complementary data analyses for fMRI: a voxel-based group-averaged approach using statistical parametric mapping (SPM) and a region-of-interest (ROI) approach analyzing BOLD responses within identified brain regions responding to our particular visual stimuli (faces and checkerboards) within each individual subject (see the results of Functional Localizers below). The latter approach enabled us to account for any intersubject variability in functional neuroanatomy of the visual system and to test hemispheric differences. Laterality effects in neuroimaging should be directly tested for with a formal comparison of effects between hemispheres, but most studies to date reported only the occurrence or absence of an effect in either hemisphere [28]. Without a direct comparison, we cannot know whether effects reportedly "absent" in one hemisphere might have been present at a slightly lower threshold.

In accord with our behavioral findings of a LVF advantage for visual targets in the context of a LVF fearful face, our fMRI results showed increased activations in right-lateralized visual areas (and more activation in the right than in the left amygdala), specifically with an emotional face presented in the LVF. This pattern was ob-

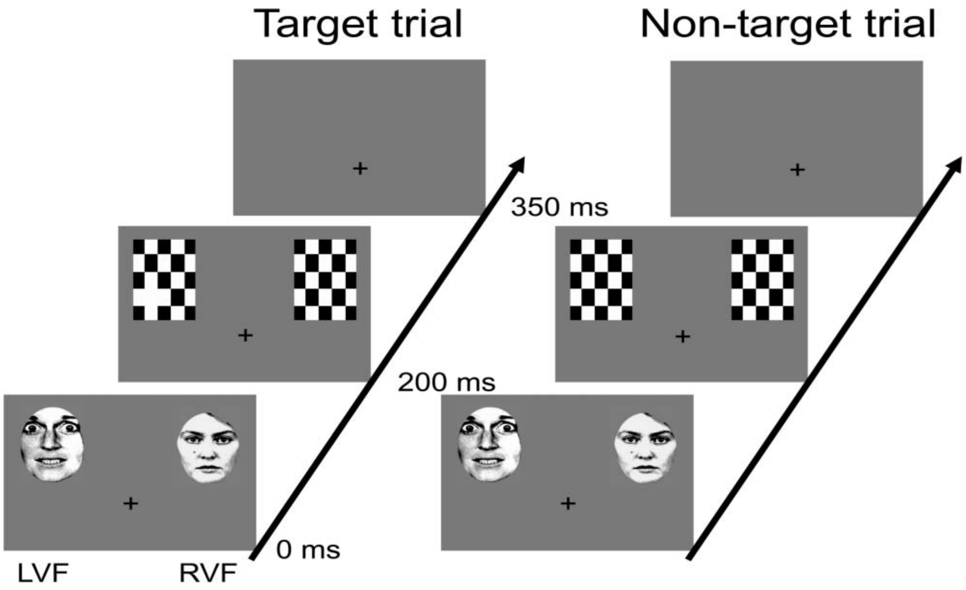

Figure 1. Example Display Sequences for Single Trials

At left, a typical sequence is shown for a "target trial." Each trial starts with bilateral faces; here, the faces have a fearful expression in the left visual field (LVF) and a neutral expression in the right visual field (RVF). The bilateral faces are followed by bilateral checkerboards, which may have one odd (deviant) square on one side; in this example, a LVF target appears with the odd square present toward the bottom of the left checkerboard, thus requiring a "lower" button-press response to indicate its elevation. Subjects had to discriminate the elevation of the odd square, regardless of its side. Face stimuli were irrelevant to this prescribed task. The righthand sequence of displays here illustrates a "non-target trial" instead (included only during fMRI scanning). To increase the number of trials per condition, 80% of the trials in the fMRI experiment were made non-target trials (hence, trials—with identical checkerboards on each side—did not have to be further subdivided by target side in addition to side of the fearful face). In the absence of an odd square (as shown in the leftmost non-target sequence), subjects did not have to make a behavioral response. However, they could not predict if an odd square would be present or absent and thus were always engaged until the checkerboards appeared.

served both in the group analyses and in analyses of subject-specific ROIs. In line with proposals that such effects on visual activations may reflect amygdala influences [19, 21], our findings revealed enhanced functional coupling between amygdala and right-anterior and middle-fusiform areas solely in the context of a fearful LVF face.

Behavioral Results

We measured speed and accuracy rates in location (upper or lower) discrimination of one deviant square (when present) among the checkerboards that immediately followed the face displays. We ran an extensive behavioral study outside the fMRI scanner ("outside the scanner") and also implemented the same task during fMRI scanning (we unavoidably collected fewer behavioral data points during scanning and thus enhanced blood-oxygenation-level-dependent [BOLD] data acquisition; see Supplemental Experimental Procedures). Data were analyzed with a repeated-measures analysis of variance (ANOVA) with factors of expression (fear or neutral), display type (symmetrical or asymmetrical), and visual hemifield (left or right). We found an equivalent behavioral pattern inside and outside the scanner, although inevitably with more statistical power outside (the statistics provided below collapsed results from inside or outside the scanner after an initial comparison showed no differences).

Mean accuracy in the square-location task was 75.2% (±2.6% standard error [SE]) and did not differ significantly ($p > 0.35$) outside (blue bars in Figure 2) or inside (red bars in Figure 2) the scanner, although the trend was for better performance outside. More importantly, there was a significant interaction between facial expression and visual hemifield [$F(1, 24) = 4.52$, $p < 0.05$], with higher accuracy for a LVF square following a fearful face in LVF than in other conditions ($p < 0.02$ by posthoc t test). This pattern was observed both outside ($p < 0.01$) and inside ($p < 0.1$) the scanner (see similar pattern for red and blue bars in Figure 2, with the first bar always showing the most accurate performance). No main effects or interactions involving the other stimulus factors (symmetric or asymmetric) were evident; hence, the effect of a LVF fearful face did not depend on the type of face shown concurrently to the RVF. Reaction time did not differ significantly across conditions (mean = 895 ± 38 ms SE). Eye position was monitored in all subjects but was not considered further because it exceeded 1° from central fixation in only 2.2% (±0.5% SE) of trials (range: 0%–5.5%) and showed no reliable differences between conditions.

Neuroimaging Results

Functional Localizers

Although the main fMRI experiment involved event-related bilateral stimulation (as in the behavioral study), we also separately used blocked unilateral stimuli (checkerboards or neutral faces) as "functional localizers" to define visually responsive and face-responsive ROIs for each subject (see Supplemental Experimental

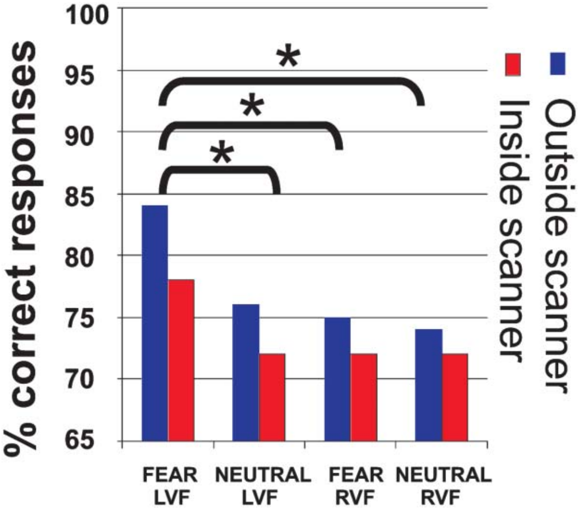

Figure 2. Behavioral Results

Percentage of correct responses in discriminating upper/lower odd squares, as a function of facial expression (fear or neutral) on the side of the odd square (LVF or RVF). Blue bars indicate percentages in the behavioral experiment outside the scanner; red bars show similar behavior for target trials during fMRI scanning. Note the better performance for a LVF odd square in the context of a LVF fearful face, both inside and outside the scanner, despite a trend for better overall performance outside the scanner.

Procedures for more details). As expected, both the checkerboards and the neutral faces activated visual areas contralateral to the stimulated hemifield ($p < 0.001$, corrected for cluster size, random-effects analysis). For checkerboards, local maxima were found in lingual gyrus, posterior fusiform, and lateral occipital areas; for faces, they were found in posterior and anterior face-processing areas in middle-fusiform and lateral-occipital areas [29] and in the amygdala at a lower threshold ($p < 0.01$) [30]).

Our ROI analyses of the event-related fMRI data focused on five visually responsive or face-responsive regions (lingual, posterior fusiform, lateral occipital, middle fusiform, and inferior/middle occipital), which were identified by the localizers and the amygdala, because our hypotheses all concerned visually responsive and face-responsive areas as well as their relation to the amygdala. Our main questions related to modulation of visual cortex by fearful faces and to any role the amygdala might have in this modulation. The critical issue is whether there is any right laterality for the fearful minus neutral (i.e., an increase of BOLD response during the fearful condition relative to the neutral condition) effects; this is expected given the LVF behavioral effect. For completeness, we first describe a conventional group-SPM analysis before moving on to an analysis of individually defined ROIs.

Group-SPM Analysis

During bilateral stimulation, presentation of a fearful face in the LVF, in contrast to a neutral face on that side, activated right-hemisphere regions in posterior and middle fusiform, middle occipital gyrus, and bilateral amygdala (note the relatively small effect in the left compared with the right amygdala; Figure 3A; Supplemental Results). No such effect was observed in any visually responsive region for fearful stimuli presented to the RVF (not even at a lowered threshold of $p < 0.05$, uncorrected). However, this group-SPM analysis only assessed voxel-wise effects and did not directly compare effects between the two hemispheres. Left/right flipping of the hemispheres of one class of images [31] before application of SPM would ignore remaining anatomical differences between hemispheres after normalization [32]. We therefore focused on subject-specific ROIs for the direct comparisons between hemispheres.

ROI Analyses

We first calculated the BOLD response for the different emotional conditions within the five visually responsive or face-responsive regions defined for each subject by the separate visual localizers (see above). Mean contrast estimates were extracted from volumes of interest (radius = 6 mm) centered at the individual local maxima of the visually responsive (lingual, posterior fusiform, and lateral occipital) or face-responsive (middle fusiform and inferior/middle occipital gyri) areas. These data were entered into a repeated-measures ANOVA with the following factors: expression (fear or neutral), display type (symmetrical or asymmetrical), hemisphere (contralateral to the stimulated hemifield), and ROI (as defined above). Critically, a significant interaction, independent of visual region, was observed between emotional expression and hemisphere [$F(1,11) = 5.81$; $p < 0.05$; see Figure 3B]. No other main effect or interaction was significant; the absence of any effect of symmetrical versus asymmetrical displays indicates that, as for the behavior, the effect of LVF-presented fearful faces did not depend on the type of face shown concurrently to the RVF. Multivariate analysis of variance (MANOVA) used instead of ANOVA (in case BOLD responses in different ROIs might be considered incommensurate) gave the same outcome of a fear × hemisphere interaction at $p < 0.05$. Post-hoc t tests revealed that the response for stimuli containing fearful faces in the LVF was significantly enhanced in comparison to those for stimuli containing neutral faces in the LVF ($p < 0.05$, Bonferroni corrected; Figure 3B) across all five regions. In ANOVA, the region factor showed only a main effect and showed no interaction involving either emotional expression or hemisphere ($p > 0.10$, not statistically significant) because the right-hemisphere ROIs all showed a similar pattern of enhanced activation for LVF fearful-face stimuli.

Similarly, a formal statistical comparison of the right and left amygdala (3-way repeated-measures ANOVA, as above) showed an interaction of fear and hemisphere [$F(1, 11) = 5.81$; $p < 0.05$], with the right amygdala showing a much larger modulation for fearful versus neutral faces ($p < 0.05$ by t test).

We investigated changes in functional coupling between the amygdala and the visual areas by testing for "psychophysiological interactions" at the random-effects level [33] and seeding at the right or at the left amygdala in SPM. Right (and, to some extent, left) amygdala showed enhanced coupling with adjacent and partly overlapping areas of the right-anterior and middle-fusiform gyrus in the context of fearful compared to neutral expression, specifically during LVF but not RVF presentation (Figure 3C: yellow indicates enhanced coupling with right amygdala, blue with left amygdala).

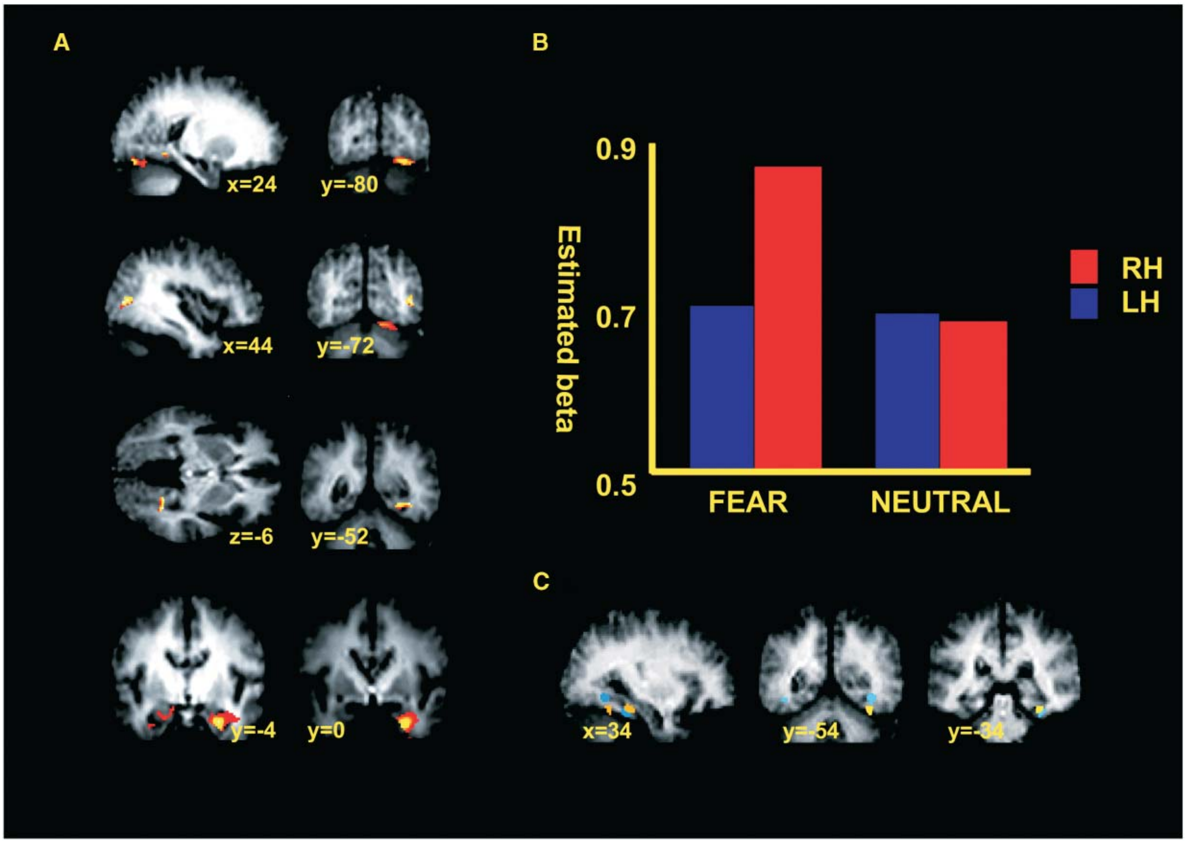

Figure 3. fMRI Results

(A) Increase in BOLD response in visually responsive and face-responsive areas for LVF fearful faces compared with LVF neutral faces at the group level in the SPM analysis (the increase is shown here thresholded at $p < 0.05$, for display purposes). The type of face in the RVF did not affect this result. Data are overlaid on the mean structural brain scans of participants.

(B) A similar pattern was found for the averaged betas (proportional to percentage of signal change) across the ROIs individually defined for each participant (sphere centered at local maximum, radius 6 mm).

(C) Changes in functional coupling in the context of LVF fearful faces: Increased coupling with amygdala was found for right-hemispheric fusiform areas (yellow areas = coupling with right amygdala, blue areas = left amygdala; $p = 0.05$ for display purposes only).

The right-posterior-fusiform gyrus did not show enhanced coupling with the amygdala directly but did show analogous coupling with anterior- and middle-fusiform gyrus (see Supplemental Data).

Our study addressed possible hemispheric differences in processing faces with fearful versus neutral expressions. We found an advantage of behavioral LVF target discrimination immediately after the presentation of a LVF fearful face during bilateral stimulation [11–13], regardless of the type of face shown concurrently in RVF. With fMRI, the behavioral effect was reflected in an increased activation of right-hemisphere visually responsive and face-responsive areas and the amygdala specific to LVF fearful faces; again, these results are specific to LVF fearful faces. Analyses of ROIs individually defined by separate blocked localizers revealed increased activation for right more than for left amygdala, for right-fusiform and lateral-occipital areas, and also for early right visual cortex; again, these results were specific to fearful face presentation in the LVF. These effects do not reflect a generic right-hemispheric advantage for all face stimuli because neutral faces did not show the laterality effects, which were revealed only by fearful minus neutral faces in LVF. A direct comparison between hemispheres for fMRI activations in the identified ROIs confirmed the right-hemisphere (RH) exclusivity for this effect of fearful faces, even though the visual localizer had shown BOLD modulation in both left- and right-hemispheric visual areas (see Supplemental Data).

Many neuroimaging studies using fearful faces failed to report fully convincing right laterality for emotional stimuli in the visual cortex. However, few used bilateral stimulus displays, which we employed here and which can maximize behavioral effects of the visual field effects [11–13]. The present laterality effect might be less pronounced with unilateral than with bilateral displays; this possibility could be studied in extensions of our paradigm.

The majority of previous neuroimaging studies of fearful faces used just single stimuli at fixation. One study did report a maxima for fearful minus neutral faces in the right-fusiform gyrus [17]; the researchers used displays that included two faces, but this analysis collapsed across “row” displays (one face in each hemifield, as here) and column displays (one above and one below fixation) and did not directly compare between hemispheres, unlike here. The right-hemispheric modulation found here in visual cortex suggests one neural correlate for the proposed right-hemispheric advantage in emotional processing. However, visual cortex might be modulated by structures processing emotional content.

The amygdala is a key area for fear processing [34, 35], and some have proposed a "limbic" prioritization system [19, 36] that may modulate perceptual processing in the visual cortex, possibly independently of the conventional frontoparietal attentional system [37]. The presence of direct anatomical connections between the amygdala and anterior visual areas [38, 39] may accord with this. In a correlational analysis of position emission tomography (PET) data, Morris et al. [19] used a blocked comparison of fearful to neutral faces and found preliminary evidence for enhanced tonic coupling of amygdala with predominantly right-sided visual areas. Our event-related fMRI data extend that early observation and indicate not only enhanced right-hemispheric activations in the context of LVF fearful faces but also enhanced phasic event-related coupling between amygdala and right-middle and anterior-fusiform areas [19, 40]; again, these results were specific to the presence of a fearful face in the LVF (see Supplemental Discussion).

The present coupling results appear to be consistent with proposals of direct feedback from the amygdala to visual regions to signal the valence of the potential threat or importance of a particular stimulus [19–21, 40]. Enhanced coupling of the amygdala and face-responsive regions without direct coupling with earlier visual areas (but see also Supplemental Discussion) may indicate a "prioritization" modulation of mid-level vision.

The behavioral results from our visual task (square discrimination) indicate that consequences of this may include enhanced processing of other visual stimuli (the subsequent checkerboard). This enhancement occurs within a short period and at the same location as the threat-associated fearful face, and it leads to enhanced activation of early visual cortex. See the Supplemental Data for evidence that the anterior fusiform, which coupled with amygdala, also showed some coupling with more-posterior visual cortex in the same condition.

In conclusion, the behavioral target-discrimination advantage that we found for the LVF after the presentation of a fearful face in that visual field can now be related to the enhanced activity revealed by fMRI in the right visual cortex and to the increased coupling that we found between the amygdala and the right fusiform in the same situation. Our findings indicate a RH advantage in visual activation when a fearful face appears in the LVF during bilateral stimulation; we observed this advantage in the context of event-related changes in functional coupling between extrastriate right visual areas and the amygdala.

Experimental Procedures

For further information, see the Supplemental Experimental Procedures.

Behavioral Experiment Outside the Scanner

Fourteen subjects (seven female) participated. Their tasks were to maintain fixation throughout the session (eye position was tracked), to ignore face stimuli that began each trial, and to indicate the location (upper/lower part) of an odd square within one of two checkerboards (Figure 1). Subjects did not know in which visual hemifield the odd square would appear. The study was approved by the Joint Ethics Committee of the National Hospitals and the Institute of Neurology.

Each bilateral-stimulus display initially consisted of two face stimuli [independently fearful or neutral (KDEF, Stockholm, Sweden, 1998, and [41]), duration 200 ms, eccentricity ±6°, lower edge 1° above horizontal meridian] followed by a pair of checkerboards (0.75° square size) for 150 ms. All possible bilateral combinations of facial expressions and side of odd-square target were used, resulting in eight possible subconditions [for faces, the "symmetrical" display types—F(ear)-LVF/F-RVF and N(eutral)-LVF/N-RVF—and the "asymmetrical" display types—F-LVF/N-RVF and N-LVF/F-RVF—were crossed with an unpredictable side of the odd-square target to yield eight possible subconditions (20 trials per condition)]. Outside the scanner, every trial had an odd-square target. During fMRI scanning, odd squares were present on only 20% of trials, so that in the scanner most events, having identical checkerboards on both sides to avoid trivial laterality in visual cortex, did not require a behavioral response (this effectively reduced the number of conditions to increase power of the fMRI study; see below).

Imaging Experiment

Twelve subjects (five female) participated. A total of 412 functional volumes covering the whole brain and a structural volume with identical slice orientation were collected in two consecutive sessions for each subject. "Nontarget trials" (i.e., without a deviant square) were introduced to increase power in fMRI analyses by reducing the number of experimental conditions and resulted in five different trial types. Four critical nontarget trial types (F-LVF/F-RVF, F-LVF/N-RVF, N-LVF/F-RVF, and N-LVF/N-RVF) were each followed by two checkerboards with no deviant square (Figure 1, rightmost sequence). Hence, these conditions did not have to be further subdivided in terms of the side of the (absent) odd square. Because the fifth target condition (20% of trials) had a deviant square, it required a discrimination response, as in the extended behavioral study outside the scanner; furthermore, it was modeled for fMRI analysis as a separate event type that did not enter the main comparisons for BOLD effects but was analyzed for behavior (Figure 2). Hence, the fMRI activations reported cannot be a confound of differential behavioral performance or asymmetric squares because there was no behavioral response or deviant square on the critical trial types for fMRI.

Volumes of the event-related session were preprocessed with SPM99 (http://www.fil.ion.ucl.ac.uk). We first modeled the responses by using the canonical hemodynamic response function [42] and their parametric modulation over time [43] for each trial type in the context of a fixed-effects general linear model. Contrasts of interest were then assessed for the group average with random-effect models at a second level to allow for statistical inference across subjects.

Visual areas responsive to checkerboards and/or to faces were identified with blocked functional localizers in the other fMRI session. The localizer activations then served as a mask for group-SPM analysis to focus on visually responsive and face-responsive regions in accord with our hypotheses. Additionally, spheres (radius = 6 mm) were centered on the local maxima for each subject, and the mean estimated beta signal estimates (proportional to percentage of signal change) from each ROI were submitted to a repeated-measures ANOVA, analogous to the behavioral analysis, or MANOVA (see Supplemental Data for functional-coupling analyses).

Supplemental Data

Supplemental Data and Supplemental Tables can be found with this article online at http://www.current-biology.com/cgi/content/full/15/5/424/DC1/.

Acknowledgments

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