In the Eye of the Beholder: Internally Driven Uncertainty of Danger Recruits the Amygdala and Dorsomedial Prefrontal Cortex

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Abstract

■ Interpretation of emotional context is a pivotal aspect of understanding social situations. A critical component of this process is assessment of danger levels in the surrounding, which may have a direct effect on the organism's survival. The limbic system has been implicated in mediating this assessment. In situations of uncertainty, the evaluation process may also call for greater involvement of prefrontal cortex for decision-making and planning of an appropriate behavioral response. In the following study, morphed face images depicting emotional expressions were used to examine brain correlates of subjective uncertainty and perceptual ambiguity regarding danger. Fear and neutral expressions of 20 faces were morphed, and each of the face videos was divided into three sequences of equal length representing three levels of *objective* certainty regarding the expressions neutral, fear, and ambiguous. Sixteen subjects were scanned in a 1.5-T scanner while viewing 60 × 6-sec video sequences and were asked to report their *subjective* certainty regarding the level of danger surrounding the face on a four-level scale combining definite/maybe and danger/no-danger values. The individual responses were recorded and used as the basis for a "subjective protocol" versus an "objective protocol." Significant activations of the amygdala, dorsomedial prefrontal cortex, and dorsolateral prefrontal cortex were observed under the subjective protocol of internally driven uncertainty, but not under objective stimuli-based ambiguity. We suggest that this brain network is involved in generating subjective assessment of social affective cues. This study provides further support to the "relevance detector" theory of the amygdala and implicates its importance to behavior relying heavily on subjective assessment of danger, such as in the security domain context. ■

INTRODUCTION

Interpretation of emotional meaning is a crucial part of understanding social context. An important component in this process is the ability to understand others' feelings and intentions by analyzing their facial expressions (Lawrence et al., 2003; Skuse, Morris, & Lawrence, 2003). Fearful expressions are particularly significant cues in this process, as they often predict the presence of a threat in the immediate surrounding (Waters, Lipp, & Spence, 2004; Mogg & Bradley, 1998). However, the meaning of facial expressions is not always clear cut, and may depend on personal idiosyncrasies and cultural codes (Huang, Tang, Helmeste, Shioiri, & Someya, 2001; Shioiri, Someya, Helmeste, & Tang, 1999), leading to individual difference in where uncertainty is aroused in the process of interpreting one's social context. Thus, uncertainty is an attribute that differs conceivably from one individual to another, and in danger situations, may result in hesitation, which hinders the ability to generate a quick and effective action. As a result, facial expressions are interpreted and variably acted upon, depending on the individual's beliefs, dispositions, and response attributes (Most, Chun, Johnson, & Kiehl, 2006; Bishop, Duncan, & Lawrence, 2004).

Consider, for instance, a situation in which, as a bystander, you encounter an unfamiliar person walking into a store, his face expressing some nervousness. He may be an innocent customer in a hurry, or alternatively, he might have criminal intentions of robbing the store. Trying to reach a decisive conclusion regarding this potential, but uncertain, threat will call for complex social cognition efforts, which, nevertheless, often result in an inconclusive decision.

Determining the meaning of a social cue from a face involves two main processes: a low-level bottom–up computation of the facial expression and a high-level top–down subjective interpretation of its intentional context.

This calls for fast and accurate computation of external information such as facial physical features and movements (bottom–up low-level processes) and integration with internally based signals (top–down high-level processes) that might also rely on previous experience. Together, these neural processes convey the integrative experience of subjective assessment regarding danger in face stimuli, rendering the decision-making in some situations inconclusive and uncertain.

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The limbic system has been long regarded as mediating such integration between information streams (Mclean, 1945, in LeDoux, 1996), and its integrity is postulated to affect the behavioral outcome of it. In primates, for instance, bilateral amygdala ablation has been associated with decreased aggression and anxiety in response to potential social threats, leading to inappropriate behavior in social encounters (Bauman, Toscano, Mason, Lavenex, & Amaral, 2006; Emery et al., 2001). Similarly, human patients with bilateral amygdala lesions judged facial expressions to be more approachable and trustworthy than did healthy subjects, suggesting the involvement of the amygdala in appraising facial features normally associated with a negative social context (Adolphs, Tranel, & Damasio, 1998). In the intact human brain, numerous fMRI studies confirmed a selective response of the amygdala to fearful and unpleasant facial expressions (Rotshtein, Malach, Hadar, Graif, & Hendler, 2001; Morris et al., 1998; Whalen et al., 1998). Although these studies may indicate a response to a certain danger, other fMRI studies suggested that the amygdala plays an important role in the evaluation of ambiguous stimuli and uncertain situations (Davis & Whalen, 2001). Cumulatively, these studies imply an interplay between the amygdala and high-order cognitive-related regions in decision-making regarding social cues in faces.

In addition to integration with the low-level process, high-order cognition is involved in the production of the most appropriate behavioral strategy in the presence of a potential danger. Such decisions are especially prominent in ambiguous or inconclusive situations where integration of prior experience and thought deduction is needed. Dorsomedial prefrontal cortex (DMPFC) has been shown in imaging studies to be involved in decision-making under uncertainty (Volz, Schubotz, & von Cramon, 2003; Johnson et al., 2002; Gusnard, Akbudak, Shulman, & Raichle, 2001; Miller et al., 2001) and in conflict monitoring (Volz, Schubotz, & von Cramon, 2005; Badre & Wagner, 2004; Krawczyk, 2002). Both these functions call for decision based on subjective criterion. Indeed, recent work put forth the idea that DMPFC also plays a role in self-generated processing, such as thoughts and intentions which might be more pronounced under uncertainty (Northoff et al., 2006; Mitchell, Banaji, & Macrae, 2005).

The main question of this study is what parameters determine danger assessment processing in the amygdala and medial prefrontal areas; to what degree is it governed by external stimulus-driven or internal observer-related parameters? We studied these options in an fMRI experiment by applying a task of danger assessment while subjects observed morphed faces with parameterized physical ambiguity regarding their fearful or neutral expressions. There is psychological evidence that dynamic (i.e., gradually changing) compared with static (i.e., same) presentation of facial expressions improves recognition of emotional states and facilitates their emotional processing (Sato, Kochiyama, Yoshikawa, Naito, & Matsumura, 2004). We therefore used short video sequences featuring gradual change of face ex-

pressions by morphing faces between their neutral and fearful expressions. Subjects were asked to assess their *certainty about the possible danger* in the surroundings of the morphed faces implied by the face expression. The paradigm thus enabled probing the effects of the objective level of expression ambiguity (ambiguous expressions in the midway morphing sequences vs. definite fearful or definite neutral expressions in the extreme thirds of the morphing sequences) versus the effect of subjective assessment of expression ambiguity (certainty/uncertainty regarding the social-related meaning of the expressions). This protocol allowed us to evaluate each face according to its objective and subjective danger-related value.

In line with the usual convention, we predicted that objectively defined fearful expressions would trigger more activity in the amygdala compared with objectively defined neutral expressions. The novel prediction was that subjective assessments of danger as uncertain would yield higher amygdala and medial prefrontal activity than subjective assessment of definite danger. The neural correlates of objective and subjective ambiguity were also examined in face-selective visual regions to test for a possible facilitation effect of ambiguity on the sensory processing of faces.

METHODS

Subjects

Sixteen subjects (7:9 male/female ratio and 27.2 ± 3.7 years of age) were recruited from a pool of psychology students and were given experiment credit for participation. All participants gave written informed consent that was approved by the Tel-Aviv Sourasky Medical Center and Tel-Aviv University ethics committees. One subject was excluded due to ghost artifacts of functional EPI images, and an additional subject was excluded due to a technical failure in acquisition of responses.

Stimuli

Colored still face images of 20 actors presenting neutral and fearful expressions were taken from The Averaged Karolinska Directed Emotional Faces (KDEF) data base (Lundqvist, Flykt, & Ohman, 1998). All figures had their hair and neck removed from the images using Photoshop software (edition 7.0.1). Each set of faces (neutral and fearful expressions of the same face) was morphed into a 6-sec-long video sequence, gradually evolving from the neutral expression to the fearful one at a rate of 40 frames per sec (morphing software, Stoik, morphman 4). The neutral-to-fear sequences were cut to three 2-sec-long video sequences designated as *neutral* (first 33% of the morphed sequence composed of frames closest to the neutral face), *ambiguous* (middle 33% of the morphed sequence, composed of frames with a blend of neutral and fearful faces), and *fearful* (final 33% of the morphed sequence,

composed of frames closest to the fearful face) (Figure 1A). The final videos included three back-and-forth presentations of each separate 2-sec sequence, thus resulting in 6-sec-long videos of facial morphs of either mostly *neutral*, *ambiguous*, or *fearful* expressions (see Figure 1C). This back-and-forth motion was driven by the need to avoid a very short or very slow-moving stimuli that would have a resulted from using a stimuli that moves only in one direction. Because stimuli were intended to be perceived as natural movement of faces from one expression to another, the velocity of movement was kept relatively high, while back-and-forth presentation of sequences were used to allow ongoing assessment of danger and accumulation of BOLD response throughout the task.

During scanning, a total of sixty 6-sec video sequences were used based on 20 different faces, each shown in three main facial expressions (e.g., neutral, fearful, ambiguous). Expression types were shown in random order interleaved with blank epochs of 6 or 9 sec in duration (Presentation software, version 8; Neurobehavioral Systems, Albany, CA). The experiment was divided into two 8.5-min-long sessions, each including the same number of facial expressions of different faces. The videos were generated on a PC and projected by an LCD projector (Epson MP 7200) onto a
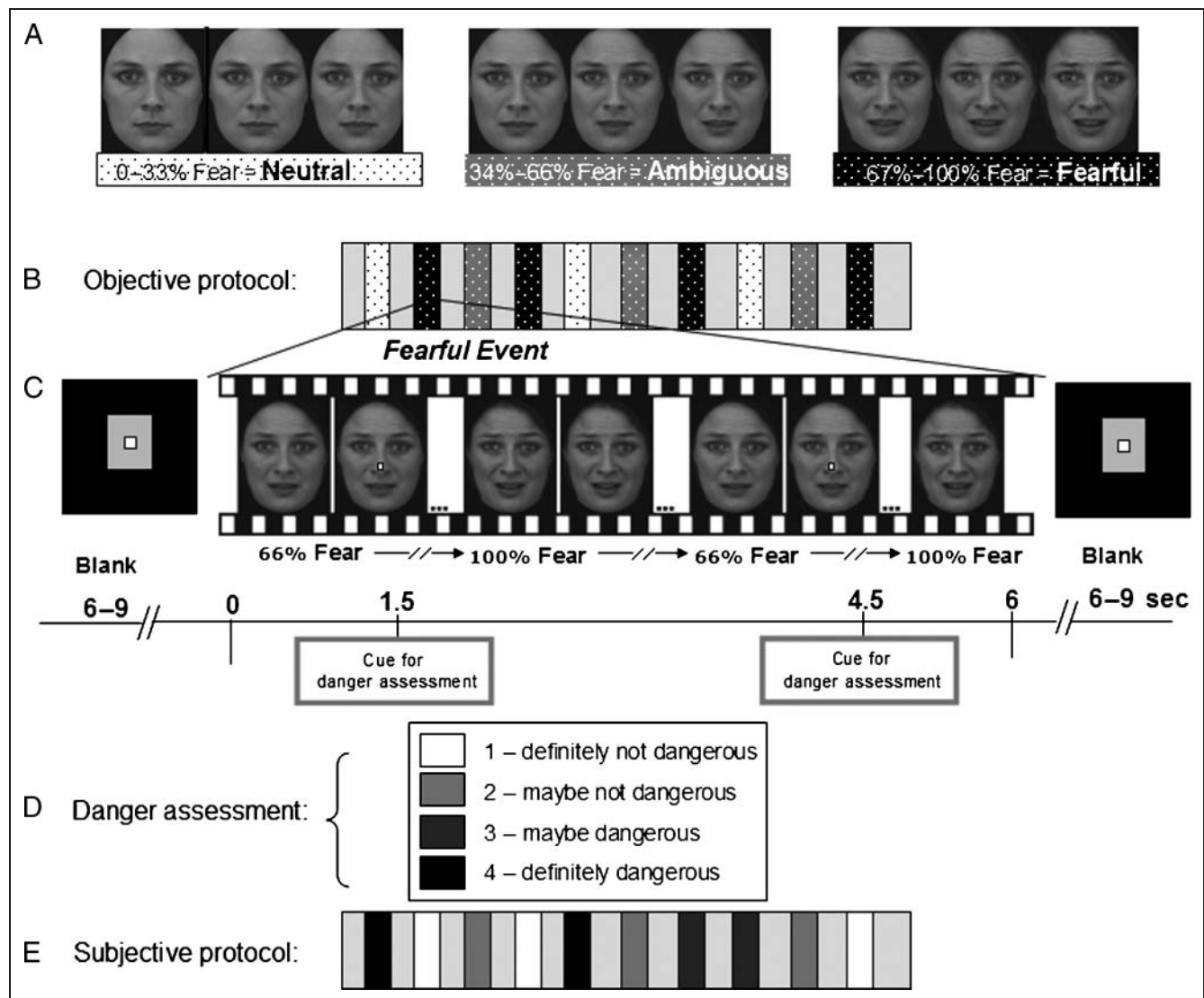

Figure 1. Experimental paradigm. (A) Examples of frames from the original movie sequence in which a particular face was gradually morphed from a neutral expression to a fearful face. Each sequence was cut to three 2-sec-long sequences designated parametrically in terms of the proportion of fearful face in the morphing; *neutral* (0–33%), *ambiguous* (34–66%), and *fearful* (67–100%). The behavioral validation of this definition is described in the results. (B) The objective protocol was based on the parametrically defined 6-sec clips (as described in A), shown in semirandom order, interleaved with blank epochs of 6 or 9 sec. (C) The composition of one fearful event as shown to participants during scanning; three back-and-forth presentations of 2 sec sequences of the fearful morphed sequence (i.e., 67–100% fearful face). Subjects were required to assess the implied danger surrounding that face twice during the event; at 1.5 and 4.5 sec from the clip onset, cued by a green dot on the face. (D) Four possible responses regarding the certainty about danger assessment, each indicated by a different color and shape. (E) An example of a subjective protocol that was designed according to one participant's danger assessment ratings.

translucent tangent screen located on a head coil on the subject's forehead. Subjects viewed the screen through a tilted mirror fixed to the head coil. In addition to the morphed face paradigm, a functional localizer scan was performed in order to pinpoint individual brain regions specifically associated with face perception in high-order visual cortex. This session consisted of twelve 9-sec blocks, each consisting of nine pictures of *faces*, *houses*, *patterns*, or *tools*, presented for 500 msec each. These were interleaved with blank blocks of 12 sec. The active voxels in the comparison of faces versus patterns were used as an ROI based on previous studies (Kanwisher, Stanley, & Harris, 1999). This region was used for detecting possible high-order visual effects in the danger assessment experiment described above.

Task

While viewing each morphed face video clip, subjects were required to assess the implied danger surrounding that face, as well as to determine their certainty about it by answering a single question. Specifically, subjects were instructed to observe the changing facial expression presented in each video and to assess the implied level of danger on a scale from 1 to 4, whereby 1 = definitely not dangerous; 2 = maybe not dangerous; 3 = maybe dangerous; 4 = definitely dangerous (Figure 1D). Thus, ratings 1 and 4 were considered as *definite* decisions regarding danger levels, and ratings 2 and 3 as *uncertain* decisions. Throughout the clip, subjects were to fixate on a black dot in the middle of the screen overlaid on the figure's face, and to respond only when the dot turned green. This question was repeated and answered twice in each sequence, 1.5 and 4.5 sec from stimulus onset (Figure 1C), to keep the subjects engaged in the task; however, only the first response was used in the following analyses. Subjects responded by pressing on a four-button response box using two fingers from each hand, the right hand pressing the right-sided buttons, and the left hand pressing the left-sided buttons, with each response category assigned to a specific finger. Score and timing of the response were recorded on-line and stored in a log-file for later processing.

During the face-related functional localizer scan, subjects were asked to perform an "*n*-back" task, that is, fixate on a dot in the middle of the screen, and think whether the picture shown was identical to the preceding picture.

Data Acquisition

Imaging was performed on a GE 1.5-T Signa Horizon echo speed scanner (Milwaukee, WI) with a resonant gradient-echo, echo-planar imaging system. All images were acquired using a standard quadrature head coil. The scanning session included anatomical and functional imaging. 3-D sequence spoiled gradient (SPGR) echo sequence, with high-resolution 1.6-mm slice thickness (FOV = 24 × 24 cm^2, matrix size = 256 × 256, TR/TE = 40/9 msec), was

acquired for each subject. The anatomical study allowed for volume statistical analyses of signal changes during the functional experiment. Functional T2*-weighted (TR/TE/flip angle = 3000/55/90°; with FOV = 24 × 24 cm^2, matrix size = 64 × 64) images were acquired (27 axial slices, thickness = 4 mm, gap = 0 mm, covering the whole cerebrum) in runs of 4590 images (170 images per slice) in the functional danger assessment session, and 2538 images (94 images per slice) in the face area localizer session.

Behavioral Data Analysis

For each subject, the mean of the first rating of each facial expression was calculated, under the assumption that the first, more than the second, rating reflected the basic decision-making process regarding the danger level. Subjective ratings were analyzed by one-way ANOVA, with face expression as repeated independent variable (neutral, ambiguous, and fearful conditions) with planned comparisons. In addition, distribution analysis of the danger assessments for facial expression type was performed to examine the frequency of assessments for each rating condition type.

RTs of the first ratings were recorded (cued by the first change of the fixation point color, i.e., 1.5 sec after stimulus) and means were calculated for the three face expressions (neutral, ambiguous, and fearful) and for the four danger ratings (definitely nondanger, maybe nondanger, etc.). RT was analyzed by one-way ANOVA for the effect of face expression and by two-way ANOVA for the effect of rating certainty (definite vs. uncertainty ratings), and rating level of danger (no-danger vs. danger ratings).

Validation of Video Sectioning

Sectioning of the original, full-length videos into three sequences termed neutral, ambiguous, and fearful was later validated using a sample of 12 subjects (5 women, 26.1 ± 3.23 years of age), recruited from a pool of freshmen psychology students, who received course credit for their participation.

Subjects viewed 26 video clips, 9-sec-long each, depicting a face whose expression changed, either from fear to neutral (N), or from neutral to fear (F), and were asked to report when the emotion depicted in the sequence changed, in their opinion. Movie clips were created from two static images of the same individual expressing fear and neutral emotions, taken from the Karolinska Directed Emotional Face set, as explained above. Stimuli were counterbalanced between subjects using a Python script (www.python.org) and presented via Presentation software, Build 10.0.07 (Neurobehavioral Systems, 2006). RTs were recorded for each subject for later analysis. In all subjects, a change in the perceived emotion was reported at $t < 6$ sec, that is, by the last third of the clip, there is no ambiguity, with variability characterizing the middle section of the clip (5000–6000 msec), as we would expect to see if the sectioning into thirds reflects a natural process of assessment. This

result was obtained both for displays progressing from fear to neutral, and from neutral to fear, validating the sectioning of clips into thirds representing fear, ambiguity, and neutrality. Average time to report change of emotion for clips progressing from neutral to fear was 4289 ± 704 msec, and for clips progressing from fear to neutral, average time to report change of perceived emotion was 4880 ± 944 msec.

Functional Imaging Data Analysis

Imaging data were analyzed using BrainVoyager 2000 software package (Brain Innovation, Maastricht, The Netherlands). Raw functional images were superimposed and incorporated into the 3-D data sets through trilinear interpolation. The complete data set was transformed into Talairach and Tournoux (1988) space of $1 \times 1 \times 1$ mm. Preprocessing of functional scans included head movement assessment (scans with head movement > 1.5 mm were rejected), high-frequency temporal filtering, removal of linear trends, and spatial smoothing (4 mm full-width half-maximum). To allow for T2* equilibration effects, the first six images of each functional scan were rejected. The two scans of the danger assessment experiment were concatenated, standardized, and treated as one experiment of 340 repetitions.

Whole Brain Analysis

Three-dimensional statistical parametric maps were calculated separately for each subject using two different general linear models (GLMs). The first GLM consisted of the three face expressions shown in the videos defined objectively as neutral, ambiguous, and fearful (Figure 1B). We refer to this GLM as the "face expression" model. The second GLM consisted of the four subjective danger rating levels (definitely nondangerous, maybe nondangerous, maybe dangerous, definitely dangerous; Figure 1E). We refer to this GLM as the "danger assessment" model. The predictor definitions from the single-study GLMs were used for calculating two multistudy GLMs for group analysis. Predictors in both models were convolved with a hemodynamic response function to account for the hemodynamic response delay. Lags were fitted for each subject based on inspection of data over several time shifts. In addition, a third GLM model was constructed, based on the subjective assessments given by subjects during the experiment, but taking into account on the first 3 sec of each event (i.e., the epoch part containing the first response) to rule out the possibility that the effects observed are the result of subjects retaining their first response in memory as a response strategy.

Active voxels were identified by contrasting ambiguous versus distinct facial expressions from the *face expression* model, and uncertain versus definite ratings from the *danger assessment* model. Mean beta values of voxel clusters achieving significance ($p < .01$, uncorrected; cluster

size > 100 mm^3) were collected for each subject and were statistically tested for more subtle effects by employing one-way ANOVA analyses on the beta values calculated from the models.

Regions of Interest

ROIs were defined in emotional, cognitive, and visual domains, focusing on limbic, prefrontal cortex, and high-order visual areas. The fusiform face area, which lies anterior to early retinotopic areas in the ventral visual stream, was defined for each subject separately based on the functional localizer session and anatomical landmarks. Only voxels in the fusiform gyrus that were significantly active in a GLM contrast comparing faces versus basic visual patterns were treated as the fusiform face area.

From the ROIs collected in the uncertainty versus definite ratings contrast, an ambiguity index was calculated based on the mean beta of each region in each of the two GLM models described above. More specifically, mean beta values of definite ratings (definitely nondangerous and definitely dangerous) were subtracted from mean beta values of uncertain ratings (maybe nondangerous and maybe dangerous), thus yielding a subjective uncertainty index. In addition, for the same regions, mean beta values corresponding to objectively distinct facial expressions were subtracted from beta values of the ambiguous expression condition, thus yielding an ambiguity index. Student's *t* tests were employed for comparing between uncertainty indices and ambiguity indices.

Correlation Maps Analysis

A correlation analysis based on "seed" time courses (e.g., see Greicius, Krasnow, Reiss, & Menon, 2003) was performed. A seed region was defined as a cluster in medial prefrontal cortex (mPFC) with the highest activation level for the uncertain versus certain ratings in the danger assessment model. Average "seed" time courses were obtained for each subject by averaging the time series of all voxels in the specific ROI. These average time courses were used as a GLM predictor to compute a voxel-by-voxel fit (analogous to linear correlation). The fit was evaluated after removing the autoregression factor (AR1 model) to account for the fact that, due to the nature of the hemodynamic response, consecutive fMRI data points of the regressor are not statistically independent. A second-level random effect analysis was applied to determine the brain areas that showed significant functional activity across subjects.

RESULTS

Behavioral Results

During the fMRI scan, participants rated the danger levels supposedly surrounding the presented face on a scale of
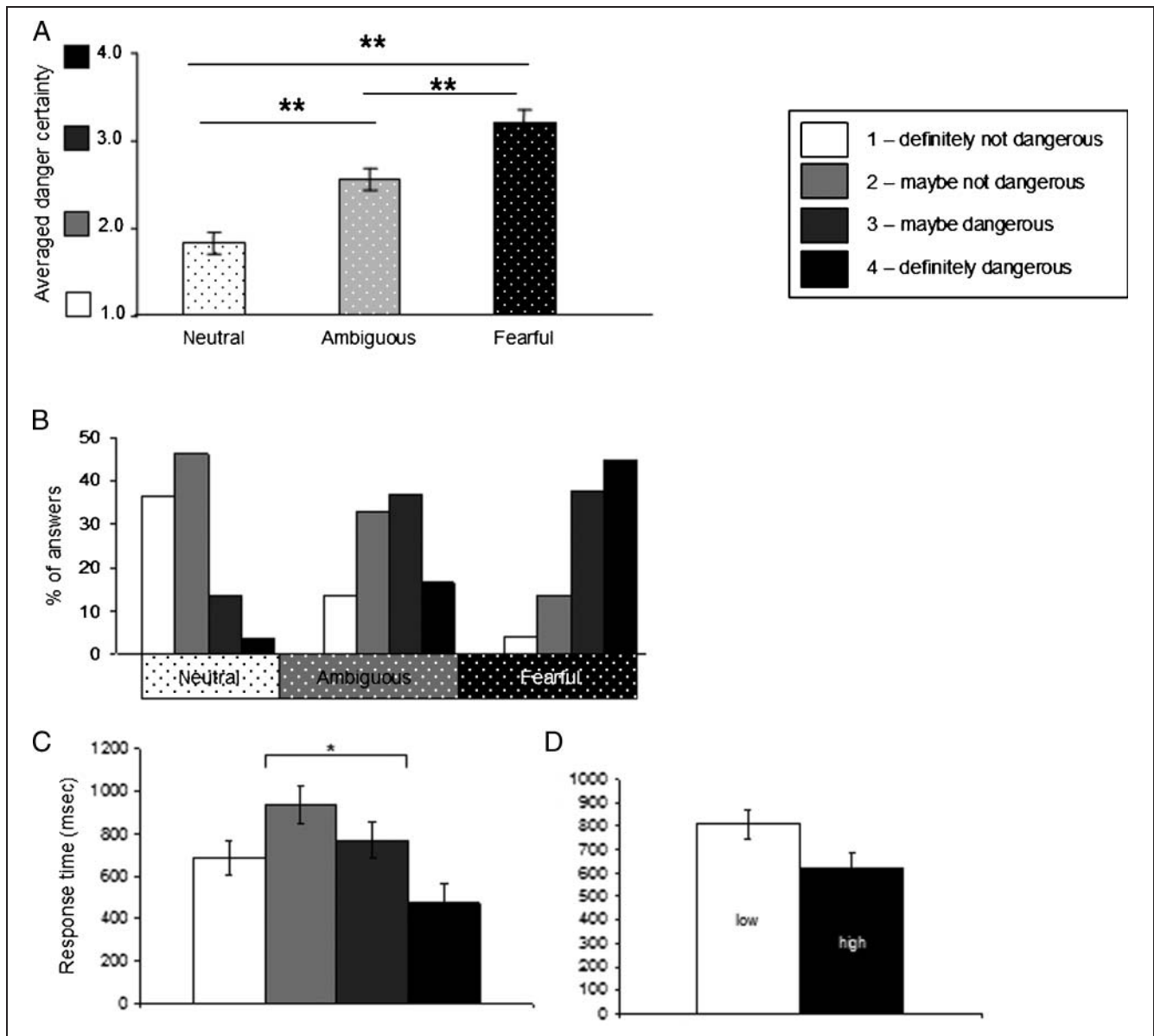
Figure 2. Behavioral measures of danger assessment. (A) The relation between objective and subjective definitions of the faces. On the average, *neutral* sequences were rated as being in least danger (i.e., rated as 1), whereas the *fearful* sequences were rated to be in highest danger (i.e., rated as 4) and *ambiguous* sequences in intermediary danger (i.e., rated as 2 and 3). All averages were significantly different from one another. (B) Distribution of subjective rating (1–4) per expression type (neutral, ambiguous, and fearful). Each expression evoked the whole range of 1 to 4 danger rating scores, with distinct answer distribution for each expression. (C) RT per danger rating score. Significant effect of rating scores on the RT with longer RTs for the uncertain versus definite ratings. (D) RT per danger rating score. Significant effect of rating scores on the RT with longer RTs for the low versus high danger ratings.

1 to 4 (definitely nondangerous, maybe nondangerous, maybe dangerous, definitely dangerous) Figure 2A demonstrates that the neutral, ambiguous, and fearful sequences were rated as being in least, intermediary, and highest danger, respectively. One-way ANOVA confirmed a significant expression effect [$F(2, 39) = 31.7, p < .001$] and post hoc Scheffe comparisons between danger assessments revealed significant differences between all three facial expressions ($p < .01$).

Despite the clear difference in rating of the three expressions, Figure 2B demonstrates that each expression

triggered the whole range of 1 to 4 danger rating scores with distinct rating distribution for each expression. Specifically, *neutral* expressions triggered mainly the "nondangerous" and "maybe nondangerous" ratings; *ambiguous* triggered mainly "maybe nondangerous" and "maybe dangerous" ratings; and finally, *fearful* triggered mainly "maybe dangerous" and "definitely dangerous" ratings. Ratings of uncertainty were found in each of the expressions, demonstrating perceptive differences between subjects and incongruence of subjective ratings and objective expressions.

Rating of danger was analyzed also in terms of RT. Average RTs ($\pm SD$) to neutral, ambiguous, and fearful expressions were 1011 ± 478, 849 ± 453, and 748 ± 510 msec, respectively. This trend of decreasing RTs for increasing objective level of danger was, however, not significant as one-way ANOVA resulted in $p = .36$.

RT was analyzed also in relation to the four danger rating scores by one-way ANOVA, using valence (dangerous vs. nondangerous) and certainty (definite vs. uncertain) as within-subject factors, respectively. Two main effects were found: a main effect for subjective certainty, revealing shorter RTs for definite versus uncertain ratings [$F(3, 39) = 6.76$, $p < .015$; see Figure 2C], and a main effect of subjective valence, expressing shorter RTs for dangerous versus nondangerous ratings [$F(3, 39) = 12.86$, $p < .02$; see Figure 2D].

fMRI Imaging Results

Whole-brain Analyses

The main goal in this study was to determine brain systems showing neural correlates to objectively and subjectively defined danger expressed by face videos. Therefore, two GLM models were constructed: a "face expression" GLM, using the objective face expressions as predictors (neutral, ambiguous, and fearful), and a "danger assessment" GLM, consisting of the subjective danger level ratings

as predictors (definitely nondangerous, maybe nondangerous, maybe dangerous, and definitely dangerous). Using the "danger assessment" model, comparison of BOLD signal to videos resulting in uncertain danger ratings (maybe nondangerous and maybe dangerous) versus certain danger ratings (definitely nondangerous and definitely dangerous) yielded activation in a network comprising of limbic and prefrontal regions, specifically the left amygdala, bilateral dorsolateral prefrontal cortex (DLPFC, BA 9) and mPFC (BA 6, 8; see Table 1 and Figure 3). In contrast, the comparison between certain danger ratings and uncertain danger ratings yielded activation in the right superior frontal gyrus (BA 8), left middle frontal gyrus (BA 10), and left middle occipital gyrus. This network of activations was preserved even when examining only the first half of the event, which contained only the first response.

Comparison of BOLD signal for ambiguous versus distinct facial expression under the face expression model yielded no activation in the amygdala or other frontal regions observed under the danger assessment model. Significant activations were observed in the right inferior frontal gyrus, right insula, and thalamus.

ROI Analyses

Figure 3 describes the results from ROI analysis for the amygdala, DMPFC, and DLPFC. Two one-way repeated

Table 1. Coordinates for Peak Activation Obtained by Main Effect Contrasts of the Subjective or Objective Model ($n = 14$, Minimal $p < .05$)

Contrast	Region	BA	x	y	z	Size	t
Uncertain > Definitive	L amygdala		−20	−3	−24	145	3.7
	L middle frontal gyrus (lDLPFC)	9	−32	29	33	167	4.3
	R middle frontal gyrus (rDLPFC)	9	33	34	35	256	5
	R superior frontal gyrus (DMPFC)	6, 8	9	15	43	750	2.9
	L inferior parietal lobule	40	−41	−54	38	373	7.1
Definite > Uncertain	R superior frontal gyrus	8	4	45	44	160	5.5
	L middle frontal gyrus	10	−38	48	−4	181	4.9
	L middle occipital gyrus	19	−38	−78	2	216	5
Ambiguous > Distinct	R inferior frontal gyrus	47	43	12	−4	242	4.7
	R insula		34	9	2	177	4.2
	R middle temporal lobe	39	37	−63	31	204	4.4
	L angular gyrus	39	−38	−57	32	270	5
	R thalamus		3	−13	8	137	4
	R inferior parietal lobule	40	43	−30	38	194	5
Distinct > Ambiguous	L occipital lobe, cuneus	18	−20	−90	17	445	6.8

measures ANOVAs of beta values collected from the activated voxels within these regions, using certainty (certain vs. uncertain) and rating of valence (dangerous vs. nondangerous) as factors, confirmed a significant increase for uncertain versus certain ratings in all of the regions: amygdala [$F(3, 39) = 3.25, p < .002$], right DLPFC [$F(3, 39) = 4.33, p < .00001$], left DLPFC [$F(3, 39) = 3.95, p < .0003$], and mPFC [$F(3, 39) = 4.14, p < .002$]. Tukey's LSD post hoc comparisons confirmed that this effect is contributed by the maybe dangerous and maybe nondangerous rating events.

Further analysis was performed on the same activated voxels, after designating the extracted beta values according to the face expression model (i.e., objective conditions of neutral, ambiguous, and fearful facial expressions). One-way ANOVA did not yield significant differences between the responses to neutral, ambiguous, and fearful expressions in these ROIs: amygdala [$F(2, 42) = 0.4$], left DLPFC [$F(2, 42) = 0.1$], right DLPFC [$F(2, 42) = 0.7$], mPFC [$F(2, 42) = 0.5$], all *ns*. Thus, it is apparent that these regions were sensitive to the subjective interpretation of the stimuli in the context of the task, rather than to the objective value of the stimuli input per se.

A predefined ROI in the right fusiform gyrus was used for analysis of the effects of facial expression or danger rating on high visual areas. The fusiform gyrus was functionally defined by contrasting faces versus patterns in the functional localizer experiment (see Methods for explanation). Figure 4 shows the ROI defined and the beta values extracted from the face expression and danger assessment models from the ROI. ANOVAs disclosed no effects of either danger assessments [$F(3, 39) = 0.65$, *ns*] or face expression conditions [$F(39, 39) = 0.3$, *ns*].

Functional Connectivity

The functional correlation analysis aimed to depict the activation network coupled with mPFC; a cortical region known to be sensitive to internally generated processing (Volz, Schubotz, & von Cramon, 2004; Volz et al., 2003). For that we extracted the time course of activation from a seed region in mPFC as obtained by the contrast of uncertainty versus certainty under the danger assessment model (BA 6/8, 26 voxels; see Figure 5A). As expected, the whole-brain analysis revealed distributed activations in the left amygdala and bilateral DLPFC, as well as regions commonly regarded as the attention network (Pessoa, Kastner, & Ungerleider, 2002), and several brain stem regions (see Figure 5B and C, respectively).

DISCUSSION

The present fMRI study was designed to investigate the relative contribution of processing objective face expressions versus subjective evaluation of the social meaning of these facial expressions to brain activity in a danger as-

sessment task. By using short video sequences of morphed facial expressions dominated by either neutral, ambiguous, or fearful expressions, and by having subjects assess their certainty about danger in the surroundings of the presented faces, we were able to distinguish between brain activation mediating the processing of the objectively defined face expressions and the subjectively assessed face-related danger context.

Danger ratings showed that the more fear the faces expressed objectively, the more dangerous the surrounding of the face was rated subjectively. Nevertheless, individual differences in degree of certainty about the danger were found within each facial expression condition (i.e., neutral, fearful, and ambiguous; see Figure 2B). This individual response distribution enabled us to investigate the neural substrates underlying subjective certainty regarding danger assessment in faces.

Decisions reflecting uncertainty about the danger, in all three face-expression conditions, activated regions of limbic, prefrontal, and parietal cortex. Specifically, activation of the left amygdala and bilateral DLPFC and DMPFC was correlated with uncertain rather than with definite decisions of danger, or with the mere presentation of fearful expressions. In contrast, definite assessments of either danger or nondanger evoked a separate network of activation, including regions in the superior and middle frontal gyrus and left occipital lobe.

Amygdala Mediation of Uncertainty regarding Danger

Our results show higher activation of the left amygdala when comparing the BOLD signal associated with uncertain versus certain assessments in all three facial expressions (i.e., neutral, fearful, and ambiguous). Thus, this amygdala activation was unrelated to the degree of fearfulness displayed in the morphed expressions, but rather to the interpretation of the supposed danger in the surrounding (i.e., context). This effect was found in whole-brain analysis as well as ROI analysis focused on the left amygdala. However, it is evident from the latter, that part of this effect is contributed by the *less-deactivation* of the amygdala when uncertainty arose relative to definite assessments (see Figure 3). This corresponds with the idea that internally generated processing, such as emotional judgment, involves regions characterized by spontaneous ongoing high activity that tend to deactivate during goal-directed tasks (Gusnard et al., 2001). Interestingly, we did not observe differences in amygdala activation when comparing fearful and neutral face sequences and assessments of definite danger versus definite nondanger. Moreover, from the ROI analysis, one can see that activation in the amygdala decreased for "definite" ratings relative to baseline; this could reflect a modulatory cortical operation following cognitive processes, which contribute to decision-making or affective labeling (Hariri, Bookheimer, & Mazziotta, 2000).
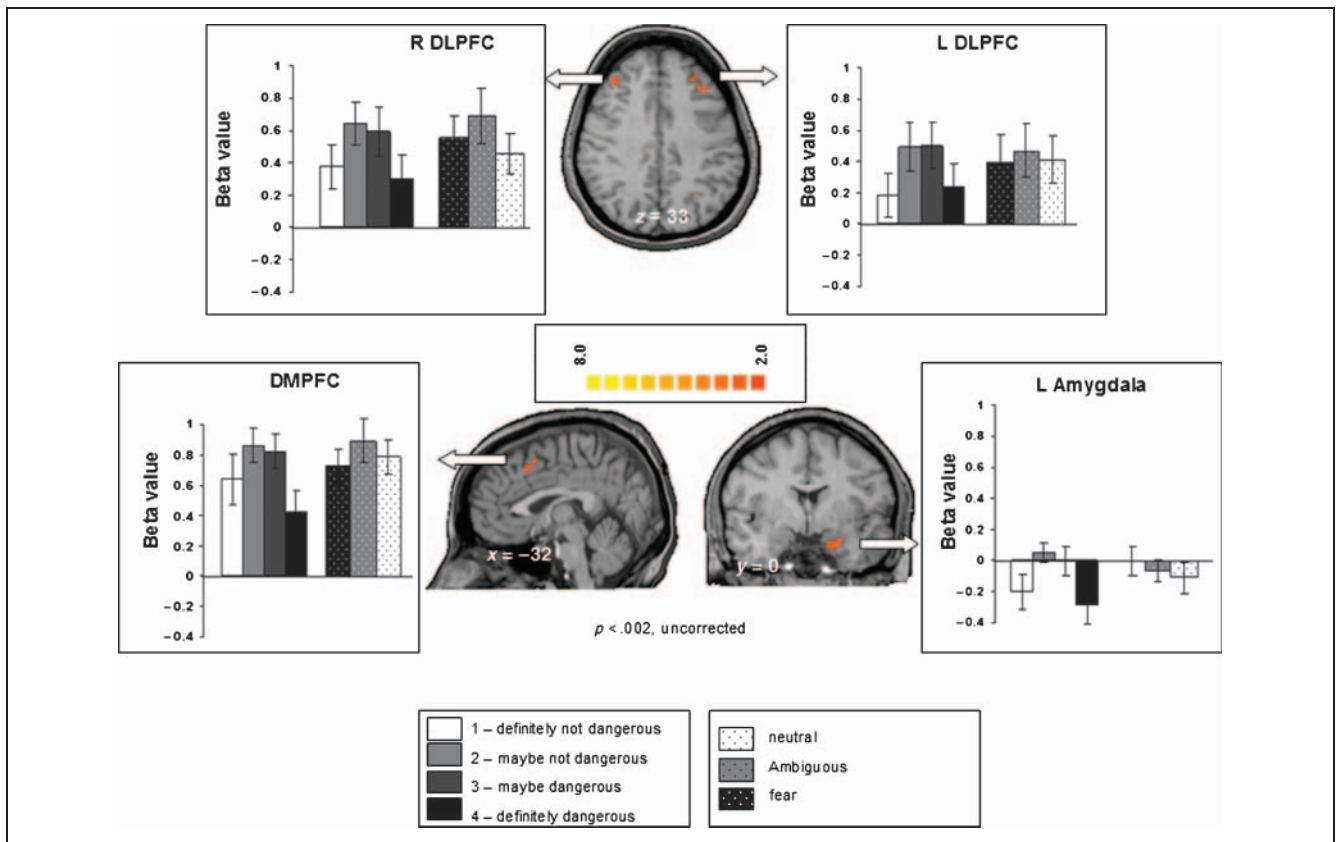
Figure 3. Activation revealed by subjective and objective protocols. Three slice views from whole-brain group activation map ($n = 14$, random, $p < .002$) obtained by the subjective protocol. Greater activation for uncertainty than certainty ratings is shown in red/orange clusters. Mean beta values ($n = 14$) were extracted from four regions of interest; left and right dorsolateral prefrontal cortex, medial prefrontal cortex, and the amygdala. Each ROI graph demonstrates the activation change obtained according to the subjective (left) and objective (right) protocol conditions.
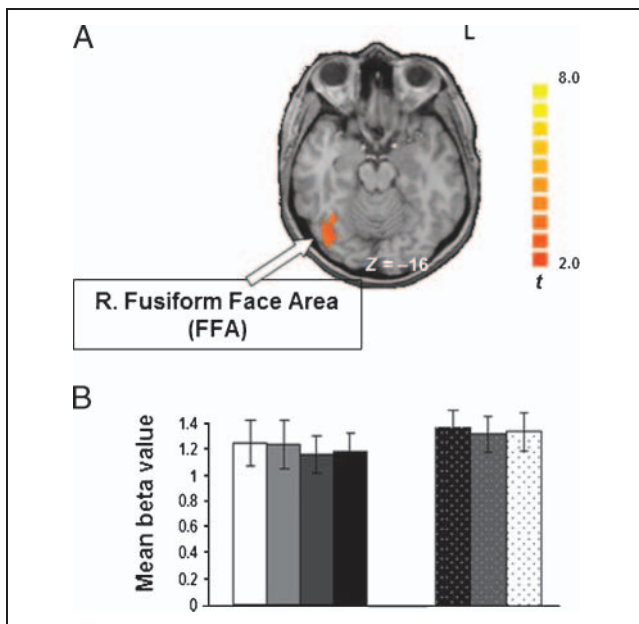
Figure 4. Face localizer activation. Fusiform face area (FFA) was defined functionally by a separate localizer scan of faces and houses. (A) Group activation map ($n = 14$, random, $p < .01$) shows the activated cluster for faces more than houses (arrow). (B) Mean beta values obtained from ROI in the FFA from the subjective (left) and objective (right) protocol conditions revealed no significant effects.
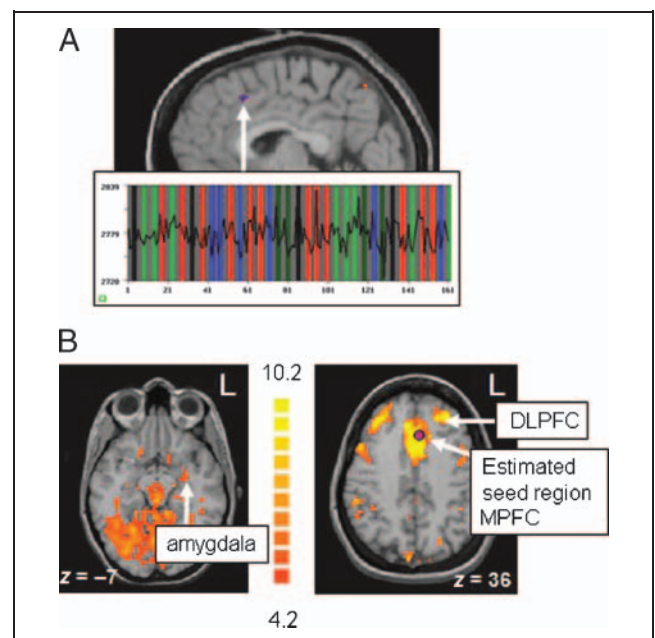

Figure 5. Connectivity analysis using DMPFC as seed. (A) A seed region (26 voxels, marked in purple) was used to study functional connectivity of the mPFC. (B) The resulting network of activation comprised the left amygdala ($n = 14$, $p < .001$; left) and bilateral DLPFC ($n = 14$, $p < .00005$; right).

Our findings suggest that the amygdala's major involvement is in formulating an opinion regarding possible danger in one's environment (Whalen, 2007). The implicated role of the amygdala in processing the intention of emotional cues is suggested by findings from a previous fMRI study in our lab (Eldar, Ganor, Admon, Bleich, & Hendler, 2007). It was shown that negatively valenced music, a relatively abstract emotional cue, induced a significant response in the amygdala only when presented together with a video which provided a concrete perceptual context.

Taken together, our findings are in line with studies that posit that the amygdala is activated most potently when sufficient data regarding a potential threat in the surroundings is lacking (Whalen et al., 1998). Specifically, in ambiguous and/or task-relevant situations, the amygdala may serve to decrease the threshold of relevant sensory systems, in order to gather additional information for resolving the ambiguity of the signal and increasing its predictability (Davis & Whalen, 2001). Furthermore, it has been assumed that the amygdala activation is inversely related to the amount of sensory information conveyed by a stimulus or the individual's certainty about its presence (Hsu, Bhatt, Adolphs, Tranel, & Camerer, 2005; Whalen et al., 1998). If the information resolves the uncertainty, the amygdala will most probably be subsided. In this way, the amygdala has a crucial role in formulating a predictive decision under uncertainty, as was proposed by others (Hsu et al., 2005). It is worthwhile to note that the amygdala was not activated when comparing conditions of ambiguous versus distinct expressions in the "objective protocol" model (see Figure 1). Thus, it seems that the objective level of ambiguity in the facial expressions did not give rise to the differentiated amygdala response.

The present findings are in contrast with numerous neuroimaging studies that implicate higher amygdala response to fearful versus neutral facial expressions when observed passively disregarding appraisal (Phan, Wager, Taylor, & Liberzon, 2004; Adolphs, 2002). Here we found that faces defined objectively as fearful did not yield greater amygdala activation than faces defined objectively as neutral. A possible explanation for this seemingly contradicting finding may lie in the nature of the stimulus and task applied in the current study. Indeed, the majority of neuroimaging studies demonstrating human amygdala response to still images of face expressions have tested implicit emotional processing by involving the subjects in gender discrimination or one-back repetition tasks (Lange et al., 2003). Several studies have demonstrated that task demands during imaging experiments can modify limbic activation patterns associated with emotional detection per se (Liberzon et al., 2000). For example, Critchley et al. (2000) applied both an explicit and implicit task using the same emotional stimuli conditions, and observed amygdala–hippocampal junction activity only in the implicit task. Similarly, Hariri et al. (2000) found decreased activation in the amygdala and increased activation in right prefrontal cortex, when comparing a labeling task of facial expressions with an implicit matching task using the same facial expressions. According to these authors, explicitly interpreting and labeling emotional expressions involves prefrontal cortex inhibition of lower limbic regions, and consequently, leads to attenuated responses of the amygdala (Hariri, Mattay, Tessitore, Fera, & Weinberger, 2003). In our case, the explicit appraisal regarding the meaning of a fearful face might recruit such prefrontal modulating mechanisms, which attenuate the amygdala's response. Uncertainty regarding the contextual danger supposedly surrounding the presented faces preserved and even enhanced the activation of the amygdala. It can therefore be cautiously suggested that the inhibitory modulation of the amygdala shown in previous studies is related to explicit tasks, which give rise to a definite resolution of the emotional parameters at hand, rather than to any tasks of implicit nature. Further support for the possible impact of uncertainty itself on the amygdala comes from a previous fMRI finding of enhanced amygdala under uncertainty regarding negative relative to more favorable consequence in a gambling game situation, more than to the negative outcome itself (Kahn et al., 2002).

As shown in Figure 3, amygdala activation was lateralized to the left hemisphere. The nature of lateralization effects are not yet well understood, but it is apparent that most functional neuroimaging studies exhibit left amygdala activation in response to visual representations of salient emotional content (Baas, Aleman, & Kahn, 2004). Moreover, Glascher and Adolphs (2003) studied patients with unilateral medial temporal lesions and reported that patients whose lesions were lateralized to the left showed reduced performance in cognitive evaluations of emotional visual stimuli. Thus, it is possible that the left amygdala takes greater part in the cognitive–social evaluation of facial stimuli, and thus, shows a discriminative response in regard to certainty of judgments in our study.

In this regard, it is interesting to note that the fusiform face area was not affected by the subject's appraisal of danger and showed a steady activation throughout the experiment (Figure 4). Analysis of voxels in the right fusiform gyrus responding more to faces than to simple patterns did not show differentiated activity between facial expressions, or between subjective ratings, exhibiting a similar activation pattern for all states. Previous studies have reported a valence facilitation effect on high-order sensory cortices when emotional attributes were of an aversive nature (e.g., Vuilleumier, Richardson, Armony, Driver, & Dolan, 2004; Morris et al., 1998). Lack of affective facilitation in our study may be related to the fact that subjects were highly attentive to all stimuli because they had to respond twice during each stimuli presented. Such highly attentive states might provide sufficient resources for visual processing in all the conditions, regardless of their affective attributes, and thus, explain the similar response pattern in the fusiform face area.

Prefrontal Cortex Mediating Uncertainty regarding Danger

Uncertainty in rating of danger activated the lateral aspect of the middle frontal gyrus (BA 9), as well as the medial aspect of the superior frontal gyrus (BA 6, 8) which is part of DMPFC. Recent fMRI studies have found that processes related to internal attributes of uncertainty due to lack of sufficient information triggered activation in mid-dorsolateral prefrontal cortex (mDLPFC) as well as medial dorsal PFC (BA 8) (Volz et al., 2003, 2004).

Present findings confirm the involvement of mDLPFC in danger assessment with regard to both the uncertainty and its subjective formulation. mDLPFC was previously shown to be primarily engaged in working memory tasking (Petrides, Alivisatos, & Frey, 2002; Levy & Goldman-Rakic, 2000; D'Esposito et al., 1998). Therefore, it is possible that the pattern of activation observed in DLPFC reflects higher working memory load in uncertain conditions. This effect may demonstrate variation in accordance with the increased demand on working memory while maintaining the same explicit task of assessing danger around a face (Rypma, Berger, & D'Esposito, 2002; Hartley & Speer, 2000; Braver et al., 1997; Smith & Jonides, 1997). The question whether this variation is related to longer decision process and/or to computational complexity due to multiple response options remains open. It is important to note that as we did not observe any difference in the activated network for uncertainty under danger assessment between the full epoch and the part containing the first response only [not shown], the effect observed here cannot be explained by a simple response strategy, whereby subjects retain their first response to repeat/change it in the second response.

DMPFC (BA 8), which was activated in the uncertain versus definite rating contrast, was previously reported in neuroimaging studies to be involved in various performance monitoring tasks (for a review, see Ridderinkhof, Ullsperger, Crone, & Nieuwenhuis, 2004). Similarly, Volz et al. (2003, 2004) observed activity in medial BA 8 when comparing uncertainty regarding outcome versus a condition that externally conveyed a certain outcome prediction. These data are consistent with our findings, implying a preferential activation of DMPFC when ratings of danger were uncertain. Moreover, Volz et al. (2004) demonstrated a parametric effect of increased activation in this area with increasing internally attributed ambiguity, which they explain to be related to an increased demand for computation on stored information (e.g., past experience); this is similarly reflected in our study in the high RT latencies for uncertainty and the activation in this area. The increase in latency of response may imply greater decision-making effort, also exhibited by enhanced activation of working memory systems, in response to uncertain stimuli. Although Volz et al. (2004) employed stimuli and tasks that are vastly different from ours and without any affective component, the two studies are comparable in that they examined internally versus externally attributed uncertainty while asking the subject to make a cognitive judgment aimed at resolving the uncertainty in the situation. It is therefore not surprising that the activations reported in these studies resemble our findings.

Taken together, the dorsal activation of the lateral and medial aspect of prefrontal cortex seem to represent a high-order cognitive effort of interpretation and decision-making during subjective uncertainty in assessment of danger. Yet, these regions also differentiate from each other as some studies suggest that MPFC is engaged in internally driven operations including performance monitoring, appraising internal goals, and self-related reflections and evaluations, whereas DLPFC is activated downstream to exert performance adjustments (e.g., response inhibition; Ridderinkhof, 2004).

The coupling observed in the connectivity analysis between mPFC, DLPFC, and the amygdala (see Figure 5) further strengthens our proposition that areas primarily engaged in relatively low-level processing of emotions such as the amygdala are recruited due to a need to resolve uncertainty in situations where reliance solely upon internally driven factors, such as past experience, is required. The involvement of arousal and vigilance in this process is suggested by the appearance of the brain stem region in this network recruitment (see Figure 5, left panel). The relative contribution of cognitive appraisal and somatic arousal to the decision-making regarding danger calls for future studies that will include physiological measurements of the subjective state of uncertainty.

In summary, it seems that formal physical ambiguity in facial expressions, by itself, does not evoke selective limbic or PFC response. Rather, internally generated uncertainty regarding the context of danger revealed substantial selective activation, mainly in the left amygdala and dorsal and medial prefrontal cortex. We therefore suggest that when looking for threat signals in a social context, uncertainty regarding these signals may be related to limbic activity, possibly mediating a high vigilant state toward a potential danger in the environment. When there's doubt regarding the emotional and social value of information, a state of high vigilance may help in recruiting the needed resource of awareness and attention in prefrontal cortex. In order to validate the assumption regarding the sequence of events, one needs to apply mapping methodologies with greater temporal resolution such as EEG and MEG. Studies employing such methods suggest that emotional stimuli undergo a coarse, relatively fast initial evaluation by limbic areas, which in turn are modulated by later prefrontal cortical areas when a higher cognitive operation is mobilized (Adolphs, 2002).

Our finding may be valuable in the security domain, emphasizing the relative impact of ambiguity and uncertainty in threat detection tasks. Nevertheless, it should be kept in mind that an attenuation of the vigilance system when the environment is perceived as dangerous might not occur in real life situations, in which danger labeling might predict

real damage or harm to the observer, calling for a survival action. Further research should examine the possible interaction between ambiguity and subjective tendencies that may influence its processing, such as mood or personality.

Acknowledgments

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