From Specificity to Sensitivity: How Acute Stress Affects Amygdala Processing of Biologically Salient Stimuli

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Background: A vital component of an organism’s response to acute stress is a surge in vigilance that serves to optimize the detection and assessment of threats to its homeostasis. The amygdala is thought to regulate this process, but in humans, acute stress and amygdala function have up to now only been studied in isolation. Hence, we developed an integrated design using functional magnetic resonance imaging to investigate the immediate effects of controlled stress induction on amygdala function.

Methods: In 27 healthy female participants, we studied brain responses to emotional facial stimuli, embedded in an either acutely stressful or neutral context by means of adjoining movie clips.

Results: A variety of physiological and psychological measures confirmed successful induction of moderate levels of acute stress. More importantly, this context manipulation shifted the amygdala toward higher sensitivity as well as lower specificity, that is, stress induction augmented amygdala responses to equally high levels for threat-related and positively valenced stimuli, thereby diminishing a threat-selective response pattern. Additionally, stress amplified sensory processing in early visual regions and the face responsive area of the fusiform gyrus but not in a frontal region involved in task execution.

Conclusions: A shift of amygdala function toward heightened sensitivity with lower levels of specificity suggests a state of indiscriminate hypervigilance under stress. Although this represents initial survival value in adverse situations where the risk for false negatives in the detection of potential threats should be minimized, it might similarly play a causative role in the sequelae of traumatic events.

Key Words: Amygdala, emotion, fMRI, human, posttraumatic stress disorder

The ability to react promptly to adverse conditions that threaten homeostasis is essential for survival (1,2). The initial phase of the stress response consists of a surge in vigilance that optimizes the detection and assessment of such threats by prioritizing sensory processing of potentially relevant (threat-related) information (3) and by reducing elaborative processing (4). Although a heightened sensitivity to threat safeguards the organism from false negatives (i.e., the failure to elicit a needed response to a potentially harmful event), it might come at the cost of decreased specificity (5). At a minimum, resulting false positives represent unnecessary, metabolically demanding responses to innocuous stimuli. However, together with an augmented alert for threat, decreased specificity under acute stress might constitute a maladaptive mechanism that sets the stage for psychological trauma etiology, as in posttraumatic stress disorder (PTSD) (6).

The amygdala is the key structure in threat detection and vigilance regulation (7). An emerging view on amygdala function is that of a gatekeeper that evaluates the environment for threat cues and facilitates enhanced sensory processing (leading to vigilance) by lowering the perceptual thresholds in relevant sensory brain regions (8), like early visual areas and the face responsive area of the fusiform gyrus (FFA) in case of emotional facial perception (9,10). In states of acute stress, vigilance is proposed to be primarily upregulated by fast-acting agents such as catecholemines that increase cellular excitability in limbic areas, predominantly in the amygdala (3). However, up to now the concepts of stress and amygdala-dependent vigilance have been studied independently and not in direct experimental conjunction. Therefore, we used functional magnetic resonance imaging (fMRI) to investigate the immediate effects of controlled stress induction on amygdala function. We examined, in particular, brain activity of participants while they performed a dynamic facial expression task—which is known to reliably engage the amygdala (11,12)—embedded in either an acutely stressful or neutral context (Figure 1A). Stressful context was induced by showing short movie clips with highly aversive content and a self-referenced instruction that directly preceded and followed the task, whereas the control condition implemented movie clips with emotionally neutral content. The dynamic facial expression task consisted of passive viewing of blocks of photographed faces morphing rapidly and dynamically into either an angry, fearful, or happy facial expression. Implementing this integrated design, we tested whether an acute, transient state of stress drives the amygdala and visual areas linked to amygdala toward increased processing of salient information (i.e., heightened sensitivity). Moreover, we tested whether stress biases these regions toward greater sensitivity to negative, threat-related material specifically or whether stress might also prime the processing of positively valenced stimuli in an unselective fashion (i.e., lowered specificity). In addition, we examined activity of the frontal eye fields (FEF) as a control region that is generally involved in the task but not expected to show a specific effect of stress.

Materials and Methods

Participants

Twenty-nine healthy women with normal or corrected vision participated in this study. Only women were included to mini-
mize heterogeneity related to gender differences in stress response (13) and neural correlates of affective face perception (14). To avoid confounds related to menstrual cycle-dependent variance in stress responsiveness (15). Scanning took place in the final 2 weeks of the cycle to ensure stable hormone levels. Participants reported no history of psychiatric, neurological, or endocrine disease and no current use of psychoactive drugs or corticosteroids. They reported no history of being victim or eye-witness of severe physical/emotional trauma or habit of watching violent movies or playing violent video games. Written informed consent was obtained before the experiment, and the study was approved by local ethical review board (CMO Region Arnhem-Nijmegen, The Netherlands) in accordance with the declaration of Helsinki.

Participants were tested in a mixed-factorial design with emotion type (angry, fearful, and happy) as within subject factor and stress induction (stress vs. control) as between subject factor. Participants were randomly assigned to either the stress (n = 14; age: 21 ± 2.1, range: 18–25) or control group (n = 13; mean age: 20 ± 1.8, range: 18–24). Data of two additional participants were excluded due to technical failure or failure to complete the procedure.

General Procedure

The experiment took place in the afternoon, to ensure low and relatively stable levels of endogenous cortisol. After arrival, participants had an acclimatization period of 1.5 hours, during which baseline saliva samples and affect ratings were collected. To avoid further anticipatory stress in the control group, participants were then told which experimental group they were assigned to before being escorted to the MR scanner. The full fMRI session consisted of several tasks that were each preceded and followed by different movie clips and thus embedded in either a continuously stressful or neutral context. In between the first two movie clips, participants performed the dynamic facial expression task reported here (see following text for description). The experiment ended with a resting condition and a structural scan. A debriefing procedure followed after participants left the scanner.

Stress Induction

In the stress condition, moderate psychological stress was induced by showing short movie clips inside the MRI scanner containing scenes with strongly aversive content (extreme violence), selected from a commercially available movie (Irreversibe, 2002 by Gaspar Noé). In contrast, participants in the control condition watched equally long movie clips from another movie (Comment j’ai tué mon père, 2001 by Anne Fontaine) that were equal in luminance and similar in language but contained only nonarousing scenes. Relative human/face presence during the movie clips was similar in both conditions (95% in neutral and 96% in stressful movie clips). Participants were asked to constantly and attentively view the movie clips (2.20 and 1.30 min, respectively) after short introductory texts put them in the scene from an eye-witness perspective, thereby attempting to involve

Figure 1. Experimental design and autonomic, hypothalamic–pituitary–adrenal axis, and subjective responses to stress induction and neutral control condition. The dynamic facial expression task (DFET) was integrated in an acutely stressful (stress group) or neutral (control group) context by means of directly preceding and following short movie clips with strongly aversive or emotionally neutral content, respectively. The task consisted of viewing blocks of emotional faces dynamically morphing into overtly angry (A), fearful (F), or happy (H) expressions (A). Stimuli consisted of short 133-msec animation clips for each of 10 different faces, showing a morphing sequence consisting of four frames (55%, 70%, 85%, and 100% emotional expression) repeated at 2 Hz. The interleaved presentation of six blocks of emotion (25 sec, 50 morphing sequences each) and nine blocks of fixation cross (25 sec, baseline for analysis) was counterbalanced across subjects and totaled 11.5 min. Averaged, baseline-corrected heart rate frequency (B) and heart rate variability (C) during movie clip 1 (light blue box), DFET (dark blue box), and movie clip 2 (light blue box) for the stress and the control group. Baseline-corrected salivary cortisol levels (D) and subjective negative affect ratings (as measured by the positive and negative affect scale) (E) assessed at baseline and at various time delays after DFET. Error bars represent SEM. bpm, beats/min. Facial expressions reprinted with permission by the Paul Ekman Group, LLC.
them maximally in the experience. This method of stress induction closely corresponds to the determinants of the human stress response as described by Mason (16), that is, unpredictability, novelty, and uncontrollability. Furthermore, it meets the criteria described by Joëls et al. (17) for stress-enhanced memory to occur, that is, close spatio-temporal proximity of stressor and task (task preceded and followed by stressor within fMRI environment) and content overlap (both employing real-life, emotionally salient stimuli). Finally, previous studies have shown that similar methods elicit measurable physiological stress responses (12, 18).

**Dynamic Facial Expression Task**

Directly in between the movie clips, participants passively viewed blocks of faces morphing dynamically into either an angry, fearful, or happy facial expression. The perceptual processing of emotional faces has been shown to robustly engage the amygdala (9) and even more so with a dynamic rather than static presentation (11). Stimuli consisted of short 133-msec animation clips for each of 10 different faces (taken from a standardized set [19] and equalized in luminance and contrast), showing a morphing sequence consisting of four frames (55%, 70%, 85%, and 100% emotional expression) repeated at 2 Hz. An experimental session lasted 11.5 min and consisted of six blocks of each emotion (25 sec, 50 morphing sequences each) and nine blocks of fixation cross (25 sec, baseline for analysis) (Figure 1A).

### Physiological and Subjective Measurements of Stress

To assess the autonomic response to the context manipulation, heart rate was continuously recorded throughout scanning with an infrared pulse oximeter (accompanying the MRI scanner, Siemens, Erlangen, Germany) placed on the left index finger. Offline artifact correction and analysis of heart rate signal, calculating heart rate frequency (HRF) and heart rate variability (HRV), was done with in-house software. The HRF was calculated as 60/mean interbeat interval and HRV as the root mean squares of successive differences between successive interbeat intervals. This method assesses high-frequency variability in HR, which is thought to result from parasympathetic action mainly and should thus show a decrease as a function of stress (20, 21). The HRF and HRV were averaged for the duration of each movie clip and task and baseline-corrected by subtracting the corresponding values derived from a resting condition, which ended the fMRI session. Data of four participants (three in the stress group) were discarded because of excessive signal artifacts.

To assess the hypothalamic–pituitary–adrenal (HPA) axis response, saliva was sampled with saliva collection devices (Sarstedt, Rommelsdorf, Germany) to determine the level of free cortisol. Sampling consisted of two baseline measurements (75 and 60 min before movie clip 1) and three additional measurements: 1) immediately after the task, 2) after the last movie clip, and 3) 20 min after leaving the scanner (15, 60, and 90 min after the start of movie clip 1, respectively). All measurements were baseline-corrected. All samples were stored at −20°C until analysis. Centrifuging at 3000 rpm for 5 min resulted in a clear supernatant of low viscosity. Salivary-free cortisol concentrations were determined by the Department of Biopsychology, TU Dresden, Germany, employing a chemi-luminescence-assay (CLIA) with a high sensitivity of .16 ng/mL (IBL, Hamburg, Germany).

Subjective state was assessed by obtaining the positive and negative affect scale (PANAS) (22) once at baseline and at three additional time-points coinciding with saliva sampling. Ten items for positive and 10 for negative affect had to be rated on a five-point scale ranging from “1—not at all” to “5—extremely”. Separate scores for positive and negative affect were baseline-corrected.

For all stress measures, statistical analyses were performed with repeated measures analyses of variance (ANOVAs) over all time points of measurement with stress induction (stress vs. control) as between subjects factor. Whenever necessary, further testing was done with simple t tests. The α was set at .05 throughout.

**Image Acquisition**

Whole brain T2*-weighted blood oxygenation level-dependent (BOLD) fMRI data were acquired using echo-planar imaging (EPI) with a Siemens TIM Trio 3.0 Tesla MR-scanner with an ascending slice acquisition (37 axial-slices, echo time [TE]/repetition time [TR]: 25/1890 msec, flip angle: 80°, field-of-view: 212 × 212 mm, matrix 64 × 64, 3-mm slice thickness, .3-mm slice gap). Three hundred sixty-three images were acquired during the task. We used a relatively short TE, an oblique axial angulation, and reduced echo-train length (23) by means of Factor 2 accelerated GRAPPA (24), to reduce artifacts caused by inhomogeneity around air-tissue interfaces. High-resolution structural images (1 × 1 × 1 mm) were obtained with a T1-weighted magnetization-prepared rapid gradient-echo sequence (TE/TR: 2.96/2300 msec, flip angle: 8°, field-of-view: 256 × 256 × 192 mm, GRAPPA acceleration Factor 2).

**Image Analysis**

Image processing and statistical analyses were performed with SPM5 (http://www.fil.ion.ucl.ac.uk/spm). The first five echo-planar imaging volumes were discarded to allow for T1 equilibration, and the remaining images were realigned with rigid body transformations. The mean image was then coregistered to the structural MR-image. Subsequently, images were transformed into common stereotactic space (Montreal Neurological Institute [MNI152 T1-template] and resampled into 2-mm isotropic voxels. Spatial smoothing was performed with a Gaussian kernel of 8 mm full-width at half-maximum.

Statistical analysis was performed within the framework of the general linear model (25). The three emotion types were modeled separately as boxcar regressors and convolved with the canonical hemodynamic response function of SPM5. Additionally, realignment parameters were included to model potential movement artifacts. Contrast parameter images generated at the single subject level (each emotion type > fixation) were submitted to second level group analysis.

Given the study’s primary focus on amygdala, this region was targeted as a region of interest (ROI). Specifically, a mask for its anatomical location in standard (MNI152) space was created by thresholding (p > .05) a probability map obtained through manual anatomical segmentation of the amygdala in the T1 images of 21 individuals (26). Anatomically based extraction of amygdala data ensures full data-independence in voxel selection and allows us to investigate all effects of interest without bias (27). The mask consisted of 127 and 107 2 × 2 × 2 mm³ voxels for the right and left amygdala, respectively. Next, mean param-
eter estimates of amygdala were extracted and entered into an ANOVA with emotion type (angry, fearful, and happy) as within subject factor and stress induction (stress vs. control) as between subject factor. The α was set at .05.

For all other regions, statistical parametric maps were created within SPM5 with a 3 (emotion type) × 2 (stress induction) ANOVA. Our statistical threshold was set at p < .05 corrected for multiple comparisons with Gaussian random field theory. Given that our additional ROIs (primary visual cortex, FFA, and FEF) do not have clear anatomical demarcations on a macroscopic level, we implemented for these regions reduced spherical search volumes (15-mm radius) centered around previously reported (functionally defined) centers: primary visual cortex (28), FFA (29), and FEF (30).

Results

Autonomic, HPA-Axis and Subjective Responses to Stress Induction

To monitor the effects of stress induction, heart rate was recorded continuously throughout scanning and salivary cortisol samples and subjective affect ratings were collected at baseline and at various time delays after the task.

The HRF and HRV, averaged and baseline-corrected separately for each movie clip and the total duration of the task, are presented in Figures 1B and 1C, respectively. A 3 (task) × 2 (stress induction) ANOVA revealed a main effect of stress induction [stress > control, F(1,21) = 15.3, p < .001] and a stress induction × task interaction [F(2,42) = 12.1, p < .001] for HRF. Separate independent t-tests additionally revealed main effects of stress induction for both movie clips [movie 1: T(22) = 3.9, p = .001; movie 2: T(22) = 4.5, p < .001] and an effect for the task that just failed to be significant [T(23) = 2.0, p = .056]. A similar analysis for HRV revealed a main effect of stress induction [stress < control, F(1,21) = 4.4, p < .05] but no interactions. Together, these results demonstrate that our stress induction resulted in elevated sympathetic and decreased parasympathetic tonus.

Figure 1D shows baseline-corrected salivary cortisol levels. An ANOVA with time as within subject factor and stress induction as between subject factor revealed that cortisol levels dropped below baseline [F(1,25) = 9.6, p < .05], most likely due to anticipation and diurnal fluctuation. Furthermore, we found an interaction between the factors stress induction and time [F(2,24) = 3.4, p < .05]. This effect was carried by a difference in salivary cortisol levels between the groups directly after the task [stress > control, T(15.8) = 1.9, p < .05, one-sided].

Figure 1E shows baseline-corrected subjective negative affect ratings as measured by the PANAS. An ANOVA revealed a main effect of stress induction [stress > control, F(1,25) = 18.6, p < .001] and an interaction between the factors stress induction and time [F(2,24) = 7.6, p < .05]. Separate independent t tests revealed significantly higher negative ratings for the stress group than the control group directly after the task [T(25) = 2.7, p < .05] and 60 min after the start of movie clip 1 [T(25) = 4.8, p < .001]. No effects of stress were found for positive affect ratings.

Together these results indicate that for the stress group the dynamic facial expression task was indeed embedded in a moderately stressful context.

fMRI Results

For the analysis of brain activity we first focused on the amygdala using a ROI analysis. We extracted mean parameter estimates of each amygdala using a predefined anatomical mask and entered these into a 3 (emotion type) × 2 (stress induction) ANOVA (Figure 2). First, as expected, the task resulted in strong bilateral amygdala activation [all emotion types > fixation] for both groups together; right amygdala: F(1,25) = 41.1, p < .001; left amygdala: F(1,25) = 30.7, p < .001. More importantly, we revealed a main effect of the factor stress induction in the right amygdala [all emotion types > fixation × stress control; F(1,25) = 9.5, p < .01], reflecting a heightened processing of emotional facial stimuli in an acutely stressful context. This main effect was qualified by an interaction between the factors stress induction and emotion type [F(2,50) = 4.3, p < .05], suggesting a differential effect of stress on the processing of facial emotions. Further testing this interaction, we analyzed the groups separately and showed a main effect of the factor emotion type in the control group [F(2,4) = 4.0, p < .05] but not in the stress group [F(2,26) = 1.2, p = .332]. Within the control group the amygdala exhibited larger responses to angry as well as fearful faces in comparison with happy faces [angry vs. happy: T(12) = 2.5, p < .05; fearful vs. happy: T(12) = 2.6, p < .05] but no difference in response to angry and fearful faces [T(12) < 1]. Taken together, this interaction between the factors stress induction and emotion type can thus be characterized as selective amygdala responsiveness to negative faces in the control group that shifted toward an indiscriminate, heightened reactivity to all facial expressions in the stress group.

An additional whole brain analysis with statistical parametric mapping demonstrated, for the main effect of face perception, robust activations in a widespread visual processing network, including primary visual cortex, extrastriate cortex, and occipitotemporal regions, like the fusiform gyrus (Figure 3, Table 1). Additionally, the task strongly activated bilateral amygdala. Furthermore, as a crucial part of the visuomotor system, involved in the allocation of spatial attention, bilateral frontal eye fields were also engaged by the task. Acute stress enhanced sensory processing of emotional faces (main effect of stress induction) in both early visual areas as well as FFA. In contrast, our FEF control region showed no differential activation. The main effect of stress in right amygdala just failed to be significant. An interaction between the factors stress induction and emotion type was exclusively observed in right amygdala. Finally, an additional regression analysis with the right amygdala as seed region revealed enhanced connectivity in the stress group between the right amygdala and midbrain (Supplement 1).
Discussion

The present study aimed to investigate the effects of acute stress on amygdala functioning. With an integrated MRI design that embedded a dynamic facial expression task in an either acutely stressful or neutral context, we found that acute stress affects the neural correlates of emotional facial processing in a twofold manner. First, acute stress drives the amygdala as well as parts of the visual system involved in face perception toward enhanced processing of emotional facial stimuli. Second, the amygdala shifts from a selective to an indiscriminate response pattern as a function of stress.

Increased responsiveness of the amygdala in acutely stressful context is associated with enhanced processing in both early visual areas and the FFA and points toward heightened sensitivity for salience of these regions under stress. Both brain regions are critically involved in (affective) face perception and have strong reciprocal anatomical connections to the amygdala (31). Furthermore, Vuilleumier et al. (9,10) have shown that the amygdala directly potentiates early sensory processing of visual stimuli in these regions as a function of emotion. The joined, enhanced activation levels observed in our data might indicate an additional modulation by the amygdala as a function of stress. As a result, this system of brain regions might contribute to a state of enhanced vigilance that augments the detection and assessment of threatening or generally salient events.

Additionally, as stress increased amygdala reactivity to equally high levels for both threat-related and positively valenced stimuli, this heightened sensitivity in the amygdala seemed to be accompanied by lowered specificity. Although recent studies also report amygdala responses to positively valenced stimuli such as happy facial expressions (32,33), larger amygdala responses to negatively as opposed to positively valenced material such as happy facial expressions (32,33), larger amygdala responses to negatively as opposed to positively valenced material is the predominant neuroimaging finding (34,35). In light of the amygdala’s putative role in vigilance, such valence-specific effects may be of interest.

Table 1. Peak Voxel and Corresponding T Values of Significantly Activated Clusters in Main Effects of Face Perception and Stress Induction and Stress Induction × Emotion Type Interaction

<table>
<thead>
<tr>
<th>Hemisphere</th>
<th>x</th>
<th>y</th>
<th>z</th>
<th>t Value</th>
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<tbody>
<tr>
<td><strong>Main Effect of Face Perception</strong></td>
<td></td>
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<tr>
<td>Widespread visual processing network (incl. early visual areas and fusiform gyrus - FFA)</td>
<td>-26</td>
<td>-80</td>
<td>-12</td>
<td>25.13a</td>
</tr>
<tr>
<td>Lateral geniculum body</td>
<td>-22</td>
<td>-26</td>
<td>-4</td>
<td>10.34a</td>
</tr>
<tr>
<td>Precentral gyrus (FEF)</td>
<td>50</td>
<td>2</td>
<td>42</td>
<td>8.16a</td>
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<tr>
<td>Cerebellum</td>
<td>8</td>
<td>-74</td>
<td>-40</td>
<td>6.79a</td>
</tr>
<tr>
<td>Superior frontal gyrus</td>
<td>6</td>
<td>10</td>
<td>62</td>
<td>6.65a</td>
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<tr>
<td>Precuneus</td>
<td>32</td>
<td>-50</td>
<td>54</td>
<td>6.37a</td>
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<tr>
<td>Superior temporal gyrus</td>
<td>12</td>
<td>-16</td>
<td>44</td>
<td>5.79s</td>
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<tr>
<td>Cingulate gyrus</td>
<td>8</td>
<td>-4</td>
<td>4</td>
<td>5.65a</td>
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<tr>
<td>Putamen</td>
<td>56</td>
<td>18</td>
<td>4</td>
<td>5.42a</td>
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<tr>
<td>Amygdala</td>
<td>22</td>
<td>-4</td>
<td>-18</td>
<td>5.26s</td>
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<tr>
<td><strong>Main Effect of Stress Induction</strong></td>
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<tr>
<td>Early visual areas</td>
<td>12</td>
<td>-82</td>
<td>8</td>
<td>3.85a</td>
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<tr>
<td>Fusiform gyrus (FFA)</td>
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<td>-2</td>
<td>3.71a</td>
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<tr>
<td>Amygdala</td>
<td>-12</td>
<td>-100</td>
<td>-8</td>
<td>3.65s</td>
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<tr>
<td><strong>Stress Induction by Emotion Type Interaction</strong></td>
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<tr>
<td>Amygdala</td>
<td>26</td>
<td>-4</td>
<td>-24</td>
<td>2.73 (p = .07)</td>
</tr>
</tbody>
</table>

MNI, Montreal Neurological Institute; FEF, frontal eye fields; FFA, face responsive area of fusiform gyrus; R, right; L, left.

a, .05 (small-volume corrected).
b, .001, uncorrected. For Montreal Neurological Institute coordinates and voxel-level statistics, see Table 1. R, right.

c, .07 (small-volume corrected).
d, .001 (Familywise Error corrected for whole brain volume).
effects are usually interpreted as resulting from the fact that angry and fearful faces convey threat in contrast to happy faces. The processing of threat-related material by amygdala is believed to be partly driven by incompletely processed, relatively coarse, low spatial frequency features of visual stimuli (7,36–38). This allows a fast, almost automatic extraction of threat signals from the environment with high levels of sensitivity but with a possible bias toward false positives (5). This vital function of amygdala might be enhanced in an acutely stressful context, geared the amygdala to higher sensitivity with less specificity. In this view, one could argue that low spatial frequency features of the dynamically morphing happy faces, like the repeated “flashing” exposure of white teeth, are overly detected by the amygdala in the stress group and conceived as potentially threatening. Recent studies show that for the evaluation of facial affect the amygdala depends mostly on affective information from the eye-region, like large, fearful eye whites (39,40). Under stress, the amygdala might additionally orient attention toward other facial regions that convey affective (and possibly threat-related) information, like the mouth. A partly complementary interpretation comes from the observation that amygdala is especially sensitive to stimulus situations that are incongruent or ambiguous and therefore in need of greater vigilance and attention (8). Accordingly, in a negative, stressful context, happy faces might get attributed a status of ambiguity that triggers high amygdala responses and subsequent sensory processing.

Alternatively but not mutually exclusive, stress might have caused reduction in prefrontally mediated control over amygdala processing, as has been previously reported in neuroimaging studies on PTSD (41,42). In this study, we did not find evidence for this, possibly because the task involved solely perceptual processing and no cognitive evaluation. For instance, we recently reported reduced prefrontal cortex activity in stressed individuals when using a demanding working memory task (4). However, it is important to consider that the absence of a negative prefrontal cortex effect does not exclude the possibility that our findings reflect, in part, reduced prefrontal control.

A potential driving force of the stress effects might be found in elevated activity of the locus coeruleus-norepinephrine system (LC-NE) (43). Given that amygdala receives direct norepinephrineergic innervation from LC (44) and NE levels in amygdala rise in response to stressful stimuli (45), one might postulate that moderately elevated baseline levels of NE in the stress group drove the observed high phasic amygdala responses. Supporting this notion, an exploratory seed region analysis demonstrated enhanced coupling between amygdala and midbrain as a function of stress. This finding is in line with recent neuroimaging studies showing that NE manipulations affect amygdala activity in humans (46–48). Through this mechanism LC-NE might promote a state of focused attention to potential stressors. However, additional studies probing directly the interplay between amygdala and LC after stress induction are needed.

A possible limitation is that we do not examine the effect of acute stress induction on the processing of emotionally neutral material. We decided not to include a previously used “neutral” equivalent to the emotional morphing faces (i.e., actors blowing up their cheeks) (33), because these stimuli have been shown to elicit strong amygdala responses, probably due to their ambiguous nature (46). Thus, these “neutral” equivalents are in that sense not truly neutral. Moreover, by restricting the study to emotional faces, we focused on the differential effect of acute stress on different emotional valences, while avoiding differences in arousal.

Finally, on a speculative basis these findings might further the understanding of stress-related mental disorders such as PTSD. Hyperresponsiveness of the amygdala to trauma-related (49) as well as generally threatening (42,50) or even emotionally neutral (51) material is found in a large variety of neuroimaging studies on PTSD (41). However, whereas most of this research encompasses the already established disease state, our data potentially elucidate some of the mechanisms related to the actual psychological trauma etiology. First, we postulate that hypersensitivity of amygdala to emotional stimuli under acute high stress might lead to exaggerated fear associations, which in conjunction with multiple other factors might develop into traumatic memory traces (6). Second, the indiscriminate nature of this amygdala hypersensitivity might relate to overgeneralization of fear associations, linking a fear response to actually innocuous information that happens to get encoded in a stressful or traumatic context and thus becomes part of the trauma. This would correspond to the clinical phenomenon of nonaversive cues being able to trigger intrusive memories and re-experiencing of the trauma, when this encoding relationship is present (52).

In sum, our data show that an experimentally induced state of moderate acute stress shifts the amygdala toward heightened sensitivity with lower levels of specificity. Although such a shift is beneficial for survival in adverse, stressful situations where the failure to detect threat might result in serious damage to the organism, it might in parallel play a causative role in the development of stress-related psychopathology.

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Supplementary material cited in this article is available online.


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